Symposium on Endocrinology of Neoplastic Diseases—Concluded

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CONTENTS

Symposium on Endocrinology of Neoplastic Diseases
(Concluded)

The Endocrine Treatment of Cancers of the Prostate Gland. Archie L. Dean, M.D., Helen Q. Woodard, Ph.D., and Gray H. Twombly, M.D., New York, N. Y. ---- 169

The Relationship of Hormones to Testicular Tumors. Gray H. Twombly, M.D., New York, N. Y. ---- 181

Adrenal Cortical Tumors—Physiologic Considerations. Allan T. Kenyon, M.D., Chicago, Ill. ---- 194

Hormonal Tumors of the Adrenal. George F. Cahill, New York, N. Y. ---- 233

The Endocrine Activity of Thyroid Tumors and the Influence of the Thyroid Hormone on Tumors in General. Jacob Lerman, M.D., Boston, Mass. ---- 266

The Endocrine Aspect of Enlargements of the Parathyroid Glands. Oliver Cope, M.D., Boston, Mass. ---- 273

Hyperinsulinism in Relation to Pancreatic Tumors. Allen O. Whipple, M.D., New York, N. Y. ---- 289

The Endocrinologic Aspects of Tumors of the Pineal Gland. Leo M. Davidoff, M.D., F.A.C.S., Brooklyn, N. Y. ---- 306

Book Reviews

Book Reviews ---- 315

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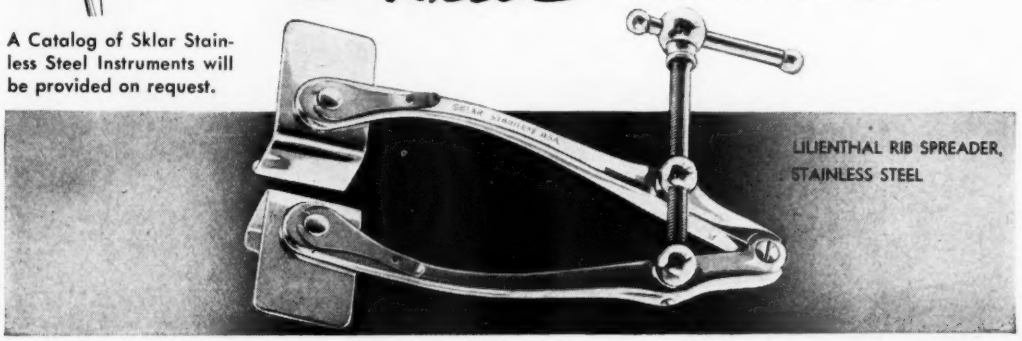

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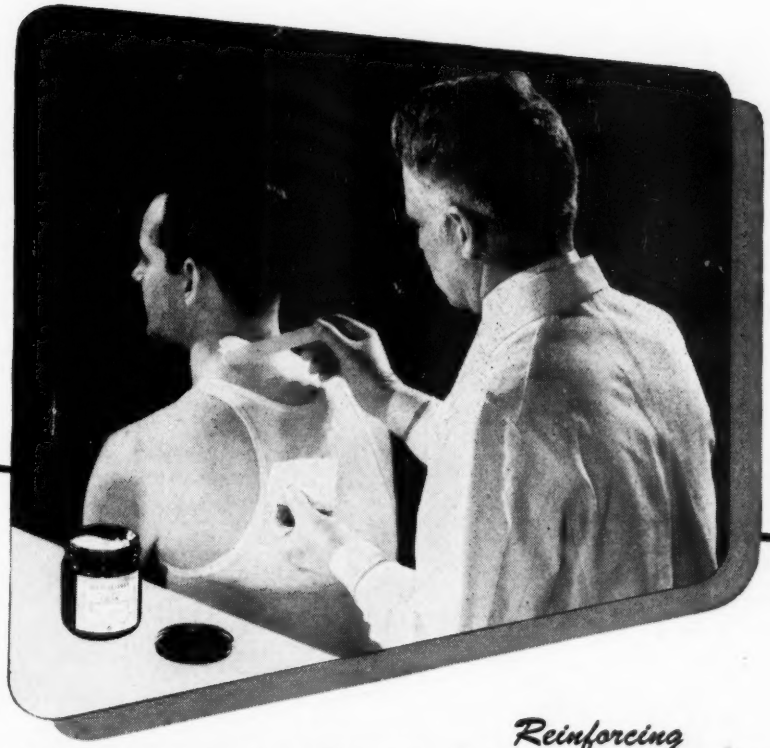

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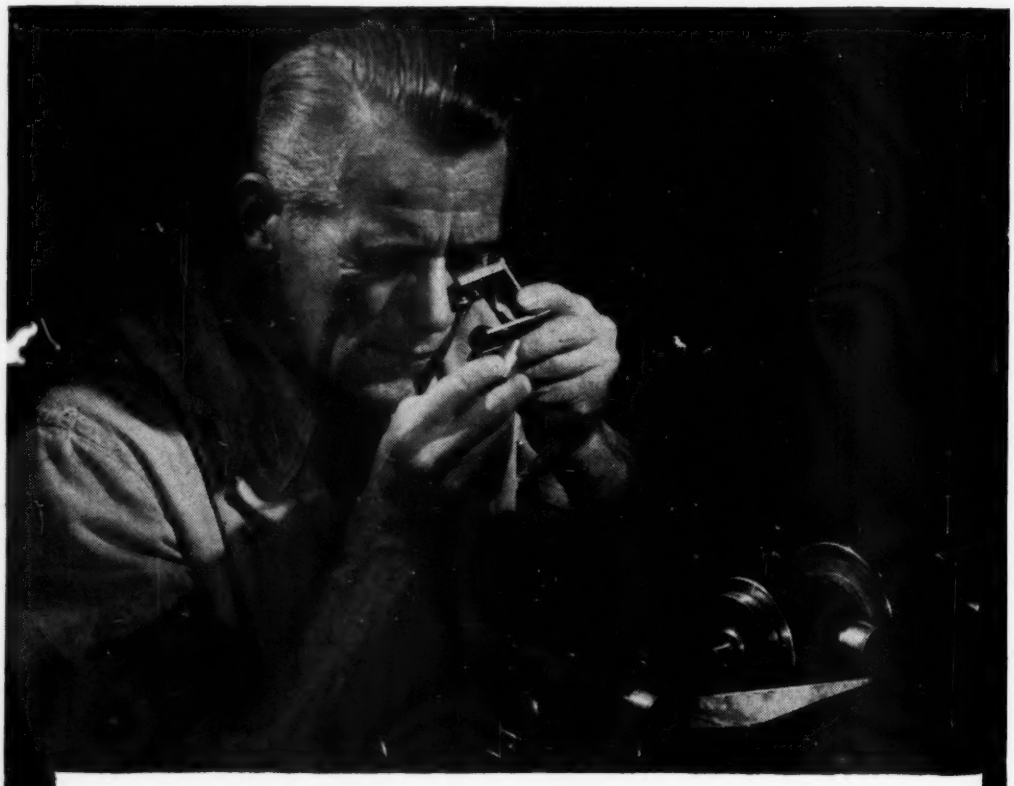

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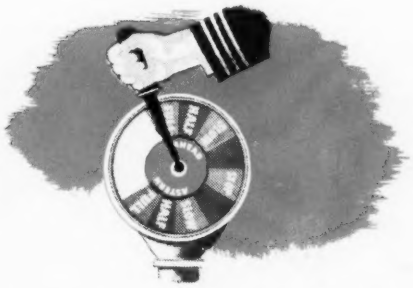

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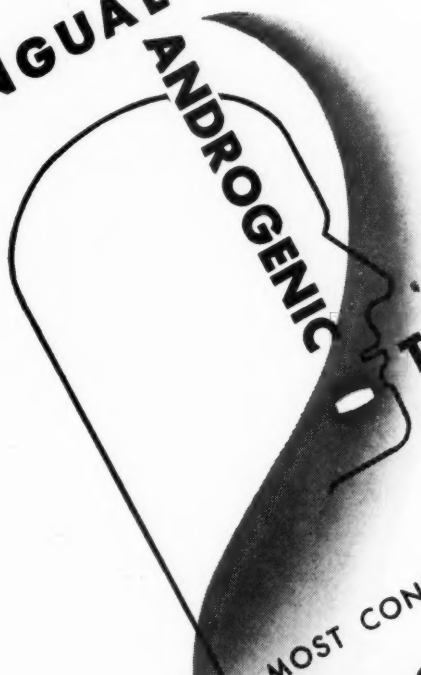

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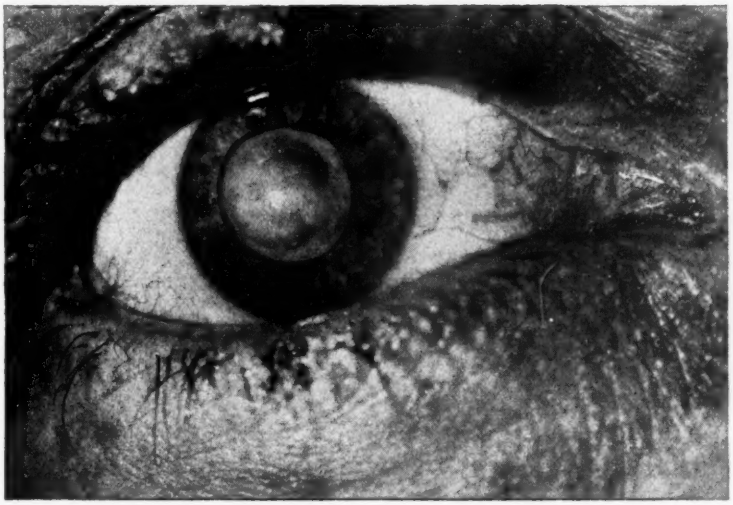

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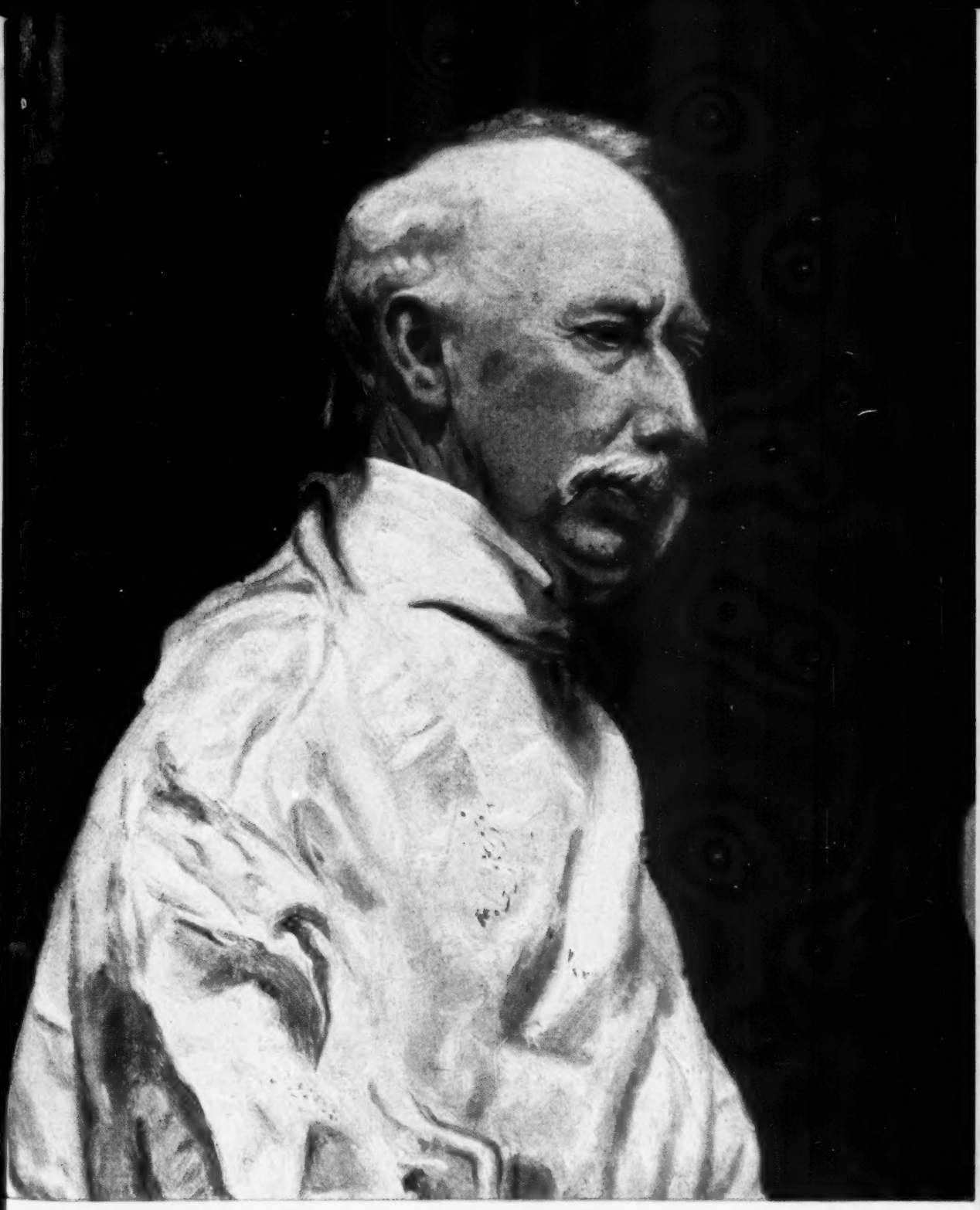

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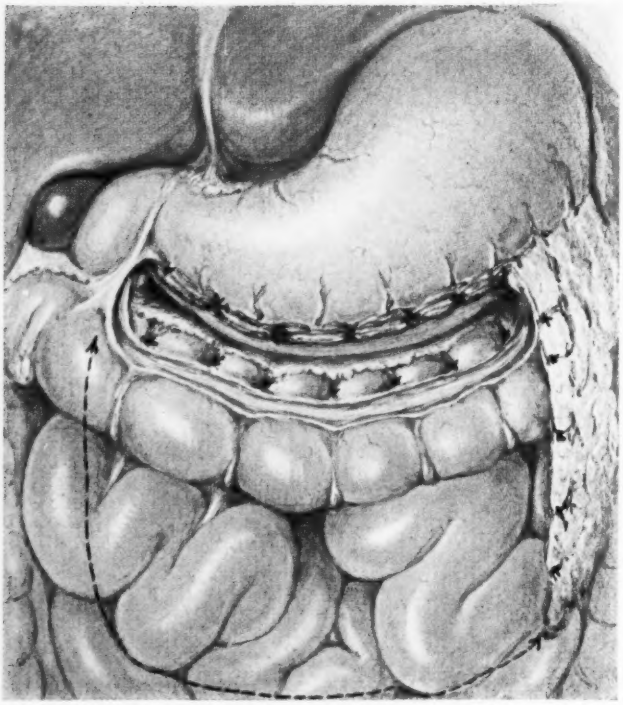

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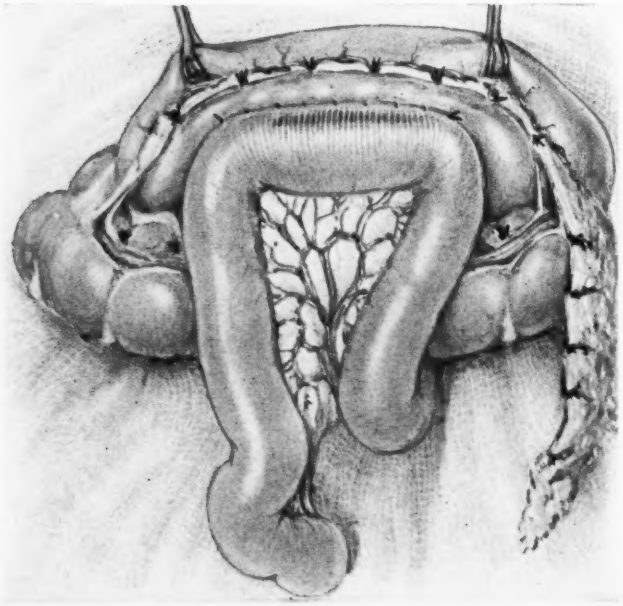

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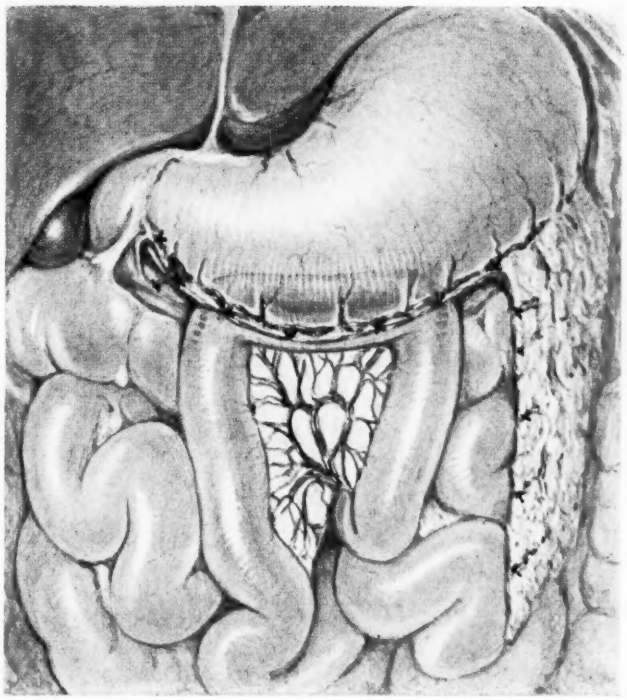

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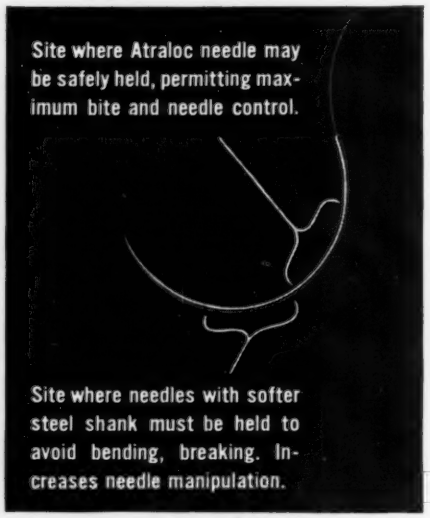
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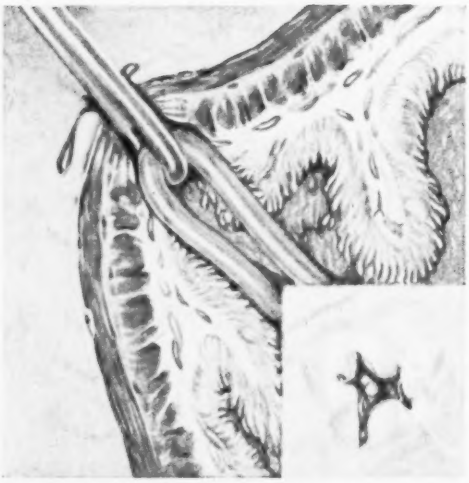

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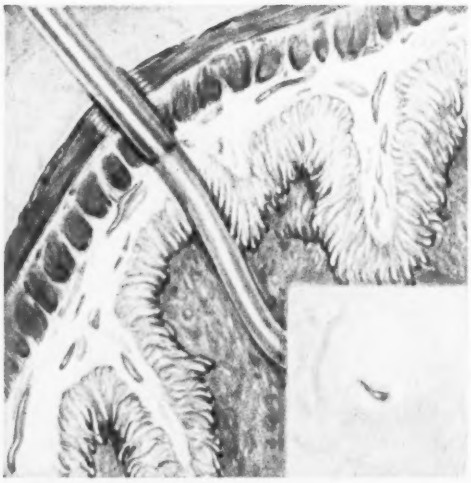

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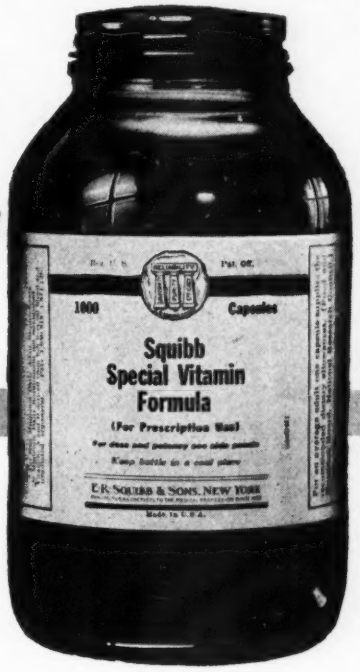

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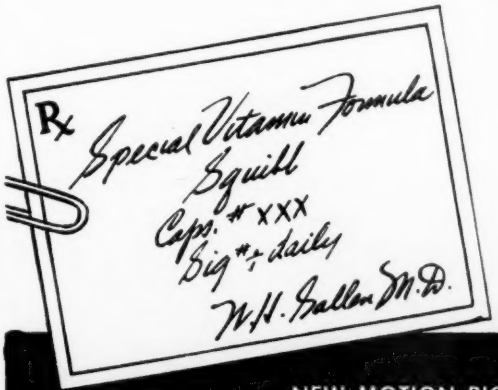

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THE ENDOCRINE TREATMENT OF CANCERS OF THE PROSTATE GLAND

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ASSOCIATION between the function of the testes and the prostate has been recognized for many years. Harvey observed that when the hedgehog hibernates the testes atrophy and the prostate also becomes smaller. He observed also that the prostates of bulls became smaller after castration. In 1893, White, on the basis of animal experiments, stated that the castration of dogs "was followed invariably and promptly by atrophy, first of glandular and then of muscular elements, of the prostate." Two years later the same worker reported the generally favorable clinical results in a group of 111 patients castrated by him and others because of prostatic enlargement. In 1898, results were reported following the castration of a number of women for cancer of the breast. Although this treatment of breast cancer never proved successful, it did stimulate further treatment of prostatic tumors by modification of the endocrines.

After a few years the treatment of prostatic enlargement by castration was largely abandoned. This was probably due to a number of factors. The majority of patients who visited physicians with bladder neck obstruction perhaps required relief more promptly than could be brought about by removal of the testes; careful pathologic differentiation between benign and malignant enlargements of the gland were not performed routinely; and finally, at this time there was greatly increased

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interest in the development of surgical methods for the relief of prostatic enlargement. For these reasons, and perhaps others, it was years before further attempts were made to treat prostatic tumors by endocrine methods. Beginning in 1934, Randall castrated five men who had prostate cancers. Since it was necessary to relieve obstruction of the bladder neck in each of these patients, transurethral resections were performed as well. Each of these patients followed a course which appeared to Randall to be what one would expect after transurethral resection alone. Therefore, the work was not reported until 1942. At about the time Randall's work was performed, or a little later, Munger irradiated the testes of a number of men with prostatic cancers. He noted that these patients did better than his other patients treated by different methods. A number of competent urologists examined Munger's patients rectally and could find no evidence of prostatic carcinoma. Beginning about 1938, a number of investigators began to treat patients with prostatic carcinomas with female sex hormones.

The development of the chemical tests, which show so accurately the condition of the patient with prostatic carcinoma that his response to treatment can be followed closely, is another phase of our subject. In 1935 Kutscher and Wolbergs isolated from the prostate a phosphatase which had its maximal activity in an acid solution. In 1936 the Gutmans and Sproul discovered that bones, the site of metastases from carcinoma of the prostate, contained this acid phosphatase in addition to the usual and well-known alkaline bone phosphatase. In 1938 the Gutmans established the fact that there was but little acid phosphatase in the prostates of infants and that this substance increased greatly with puberty. These workers found acid phosphatase in the normal adult prostate, the hyperplastic prostate, and the cancerous prostate. More recently, Gomori, through his microphosphatase tests, demonstrated that acid phosphatase was present only in the adult epithelial cells of the gland. This was the first demonstration of a chemical secondary sex characteristic.

After this pioneer work, assays of the serum acid and alkaline phosphatases came into general clinical use, and their accuracy in diagnosing cancers of the prostate and estimating the extent of the disease has been proved. More specifically, on the basis of the phosphatase findings, four groups of patients have been recognized:

1. Normal men in whom there is no increase in either the serum acid or alkaline phosphatases. It is noteworthy that since every adult prostate contains large quantities of acid phosphatase and that the serum acid phosphatase of men is the same as that of women, who have no organ rich in acid phosphatase, this substance is prevented from entering the circulation by an intact prostatic capsule.

2. Patients with cancers of the prostate and normal amounts of serum acid and alkaline phosphatase. In this small but definite group one may

operate with an excellent chance of removing all of the disease because the tumor probably has not grown beyond the gland.

3. A group consisting of the great majority of patients with prostatic carcinoma. The tumor has grown through the gland capsule and there may or may not be distant metastases. In our experience 73 per cent of these patients show increased serum acid phosphatase.

4. Patients with prostatic cancers which metastasize to bones. There is nearly always an increase in the serum alkaline phosphatase in these cases. The quantity of this substance in the serum so accurately represents the amount of reaction of the bones to the invasion of prostatic carcinoma that quantitative assays give clinical information not obtained by any other tests, such as the roentgen rays.

From the clinical standpoint, cancers of the prostate have long been considered incurable. The frequency of the disease was well recognized and it had been closely studied by many investigators. Radical operations had been devised for removing all of the affected prostate gland with adjacent structures; external radiation from the most efficient sources had been used in many cases, and interstitial radiation had been employed frequently, with radon seeds implanted both through perineal and suprapubic approaches. In spite of the most careful use of these forms of treatment, the clinical results seldom showed more than various degrees of palliation. It was against this background of deserved pessimism that the announcement of Huggins and his coworkers stood out in marked contrast. This investigator reported that after the relatively insignificant operation of castration, patients with advanced prostatic cancers improved in general, their primary tumors became smaller, and metastases regressed.

Huggins' clinical work was based on a long series of ingenious animal experiments. Dogs' prostates were isolated from their bladders and a study was made of the normal excretion of prostatic fluid. It was then demonstrated that the administration of androgens stimulated prostatic activity and increased the flow of prostatic fluid. It was shown also that the administration of estrogens promptly stopped the production of prostatic fluid. It was learned that the administration of androgens caused hyperplasia of the epithelial cells of the prostate and that, in some cases, metaplasia became so marked that the appearance of the gland simulated cancer. When estrogens were given, these glands promptly returned to normal. Huggins also showed that after surgical castration prostatic secretion stopped and metaplasia of the epithelial cells regressed.

As soon as this work was reported we began the endocrine treatment of patients with prostatic cancers and treated each case like any complex clinical research problem. We have attempted to give our patients every benefit from modification of the endocrines, and at the same time we have attempted to learn the factors which bring about the clinical changes and the nature of these changes. We have, therefore, stud-

ied carefully each patient from the clinical, chemical, and endocrinologic viewpoint. In addition to frequent clinical and roentgenologic examinations before and after treatment, at short intervals routine assays have been made of the acid and alkaline phosphatases, phosphorus, calcium, and chlorides of the blood, and of the creatinin, androgens, estrogens, and gonadotropic hormones excreted in the urine. Our clinical experience with the endocrine treatment of prostatic cancers is based on approximately 100 cases. Of these, about 40 have been observed for only short periods, or have been lost to follow-up. Sixty patients have been observed for six months or more or have died within six months after they were first seen. Thirty-one were treated by surgical castration and twenty-nine by stilbestrol. As these groups are small, statistical studies would be misleading and will not be attempted.

In our experience, surgical castration almost invariably has given prompt relief to patients with prostatic cancer. The improvement of patients with hopelessly far advanced disease is one of the most spectacular changes to be observed in clinical medicine. In no case did we withhold orchiectomy because of advanced disease, although many patients seemed near death at the time of operation. In a number of instances, patients had been confined to bed for months because of pain due to metastases. Frequently they had acquired serious contractures of their lower limbs. It was surprising, but not at all unusual, to see these individuals learning to walk within a few days of operation. Almost without exception, pain disappeared within forty-eight hours. In the majority of cases it had almost gone within twenty-four hours. Appetites became remarkably good, body weight increased rapidly, strength returned, and a large proportion of the men resumed their former occupations and could engage actively in sports. Regression in the size of metastases to soft parts was prompt. Large suprapubic masses, proved cancerous by biopsy, completely disappeared within two weeks of castration. Similarly, metastases in lymph nodes could no longer be felt from two to three weeks after operation. In a number of instances, metastases in the lungs could no longer be demonstrated a short time after treatment. After orchiectomy we were able to show diminution in the size of the primary prostatic tumor only occasionally, and we usually failed to observe a decrease in the amount of residual urine. Roentgenograms of the skeleton were made at trimonthly intervals, but changes in the roentgenographic appearance of the bones were difficult to interpret. The usual metastasis in bone from a prostatic carcinoma is shown as an area of increased bone density. As the patient improved and healing took place in the bone, one would expect a still further degree of bone density to be produced. We feel that we have not had sufficient experience in observing these changes to recognize the clinical status of bone lesions accurately by their roentgenographic appearance. On the other hand, we have seen patients, apparently greatly benefited by castration, in whom bone metastases seemed to be spread-

ing. We also observed what appeared to be improvement in a metastatic area on the right side of a pelvis, while at the same time, an obvious metastasis appeared and grew larger in the left pelvic bones of the same patient. We believe that in a certain proportion of patients bone metastases improved substantially, but just how frequently this occurs we are unable at present to state.

After a varying period of apparently good health, which, on the average lasted eight months, the majority of our castrated patients relapsed. Usually the relapse was first suspected because pains recurred. Phosphatase assays also indicated a relapse at about the same time that it was apparent to clinical observation.

While the great majority of castrated patients improved, a certain small percentage continued an uninterrupted downhill course and died a short time after operation.

Histologic studies of the testes removed from our patients, in practically all cases, showed moderate tubular atrophy with from slight to marked interstitial cell hyperplasia. All of the testes we removed appeared grossly within normal limits.

After observing so many relapses following castration, we began to treat a larger proportion of our patients with stilbestrol, administered by mouth. Although this drug sometimes causes nausea and vomiting, our patients had little difficulty if 1 mg. was taken daily at bedtime. While the improvement in these patients was not as sudden as that which followed castration, at the end of a few weeks the majority seemed as well in all respects as those patients who had benefited most by castration. In this group we were able to observe a greater degree of regression in the size of the primary prostatic tumor with a corresponding reduction of the amount of residual urine. These beneficial changes appeared to be correlated with and generally in proportion to the amount of feminization brought about. Breasts enlarged and they sometimes became tense and painful. The nipples and areolae turned dark brown. Later there was likely to be an accumulation of weight about the hips. After an average period of seven months, patients treated with stilbestrol relapsed. However, up to the present time, a much smaller proportion of patients have relapsed under stilbestrol therapy than after castration, and those patients who did not relapse after stilbestrol therapy enjoyed excellent health on an average of two years after treatment was begun.

After the castrated patients relapsed, we treated them with stilbestrol, and after the patients treated with stilbestrol relapsed, we castrated them. Although these groups are too small at present for close analysis, neither type of secondary treatment proved successful.

It is of interest to attempt to correlate the chemical and endocrinologic changes with the clinical courses of these patients. Fig. 1 shows the changes which took place in the acid and alkaline phos-

phatases, in the chlorides and calcium of the serum, and in the excretion of the estrogens and androgens of a representative patient following orchiectomy. This man had unusually extensive bone metastases. He did well for eight months and then underwent a clinical relapse with coincident rise in both acid and alkaline phosphatase to pretreatment levels.

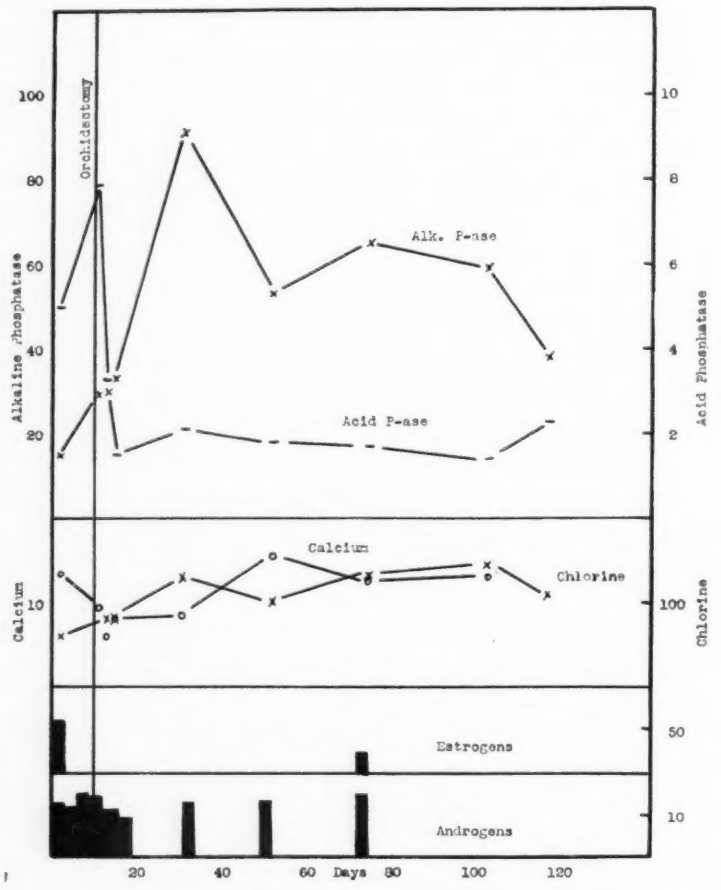

Fig. 1.—Acid and alkaline phosphatase in units per 100 c.c.; calcium in milligrams per 100 c.c.; chlorine in milliequivalent per liter; estrogens in mouse units excreted per seventy-two hours; androgens in milligrams excreted per seventy-two hours.

The acid serum phosphatase rose above the initial level on the first postoperative day and then dropped abruptly, but remained above normal throughout the period of observation.

The alkaline serum phosphatase rose rapidly, reaching five times the initial value three weeks after castration, and then exhibited a slow downward trend. During this time the metastatic areas in the bones increased in size, number, and degree of osteoplasia.

The serum protein and inorganic phosphate showed only minor changes and are not shown in the illustration.

The serum calcium dropped to abnormally low values immediately after castration and later returned to normal. This is a frequent finding, the significance of which is not yet apparent.

The serum chlorine paralleled the alkaline phosphatase throughout. This parallelism has been observed in several patients, and may indicate a relation between the adrenals and alkaline phosphatase.

Estrogen assay was unsatisfactory owing to the toxic effect of the urine of this patient on mice, but there is evidence that estrogen excretion fell after castration.

Androgen excretion showed a transitory fall after castration, and then rose to the initial values.

The acid and alkaline phosphatases in the serum of our patients were determined by a modification of the Bodansky method which is described elsewhere. Sodium-β-glycerophosphate was used as substrate throughout. Normal values for acid phosphatase were from 0 to 0.7 units per 100 c.c. of serum when the alkaline phosphatase was normal or as high as 0.9 units per 100 c.c. when the alkaline phosphatase was high. Values above 1.0 unit per 100 c.c. were considered pathognomonic of metastasizing prostatic cancer. Normal values for alkaline phosphatase were from 1.5 to 5.0 units per 100 c.c. While increased acid serum phosphatase indicates an extension of a prostatic cancer, a normal quantity of acid serum phosphatase occasionally is found in the presence of an extensive tumor. However, while false negative tests may occur, increased acid phosphatase has not been found except with this disease.

In describing the results of our phosphatase assays, we have omitted patients on whom we had no adequate readings prior to treatment, those who received radiation at such a time as to influence phosphatase determinations, and those who were lost to observation within a month after treatment was started. With these exceptions we have records of the acid and alkaline phosphatases of the serum before and after surgical castration of 26 patients with prostatic cancers.

In 19 of the 26 patients the acid serum phosphatase was elevated before treatment was given. In 16 of the 19 the quantity diminished during the two months which followed castration. While it seldom reached normal, the decrease in acid phosphatase usually was striking, amounting in one case to a change of from 115.0 to 1.4 units. In 3 patients there was no significant change in acid phosphatase after castration. Two of these men failed to show clinical improvement after operation and soon died. In the third, only a borderline abnormality in acid phosphatase was present. Seven patients had a normal acid phosphatase before treatment and no remarkable changes could be observed after castration.

In a group of 23 patients treated with stilbestrol we found changes in acid serum phosphatase similar to those which followed castration.

Our experiences, therefore, confirm Huggins' findings and offer clear-cut evidence that withdrawal of testicular hormones or administration of estrogens, for a time at least, causes a marked reduction of acid serum phosphatase. Presumably this may be brought about either by diminishing the production of acid serum phosphatase by the prostatic cancer or by lessening the ease with which this enzyme enters the circulation. In patients in whom acid phosphatase does not enter the circulation neither castration nor administering stilbestrol causes it to do so.

Of the 26 patients who were surgically castrated, the preoperative assays of alkaline serum phosphatase were elevated in 17. All but 1 of these men had definite evidence of bone metastases. In 11 of the

17 after castration there was a further rise in alkaline phosphatase at some time during the following two months. In the remaining 6 patients the alkaline phosphatase either did not change or it decreased. Sixteen of 22 patients who were treated with stilbestrol had pretreatment elevations in serum alkaline phosphatase. Of these, only 4 showed a further rise in alkaline phosphatase levels; in the remainder there was no change or a slow decrease.

Nine patients had normal preoperative readings of serum alkaline phosphatase. In 4 of these patients there was definite evidence of bone metastases. In 3 of the 4 there was a significant rise in alkaline phosphatase after castration.

In the patients who have been observed long enough for roentgenographic changes to have become demonstrable there usually has been a marked increase in the degree of osteoplasia whenever there has been a rise in the alkaline phosphatase. In some cases this appeared to indicate healing, while in others pre-existing metastatic areas have grown larger and new metastatic areas have appeared. In at least 4 patients in whom a fall in alkaline phosphatase has occurred after an initial rise, the fall apparently has been associated with extension of the metastases. We have been able to find no correlation between changes in either estrogen or androgen output and alterations in either of the serum phosphatases.

Considerable evidence has been produced by one of us (H. Q. W.) and by others to show that alkaline phosphatase is produced in excess by bone as a defense mechanism. This is a nonspecific response, and may be the result of deficient supplies of calcium and phosphorus, as in rickets; of loss of calcium and phosphorus, as in hyperparathyroidism; or of injury, as in metastatic disease. When prostatic carcinoma has invaded bone, the activity of the injurious agent (prostatic carcinoma) is reflected in the degree of elevation of the acid phosphatase in the blood. The activity of the bone defense is indicated by the amount of alkaline phosphatase in the blood.

After castration the activity of the prostatic cancer in bones probably decreases as is shown by the drop in acid phosphatase. We should expect that the alkaline phosphatase, an index of the attempt at bone repair, would also decrease as the need for repair became less urgent, and would reach normal, several months later, when repair was well advanced. This has occurred in a few of our patients. As previously indicated, however, in the majority of cases the alkaline phosphatase rises rather than falls in the first two months after castration. Three possible explanations of this reaction may be suggested:

1. There may be no increase in the production of alkaline phosphatase, but instead there may be an increased rate of diffusion of this enzyme into the blood. This is unlikely in view of the close relationship between assays of alkaline serum phosphatase and bone activity.

However, certain osteogenic sarcomas contain abundant alkaline phosphatase which does not enter the circulation. Hence, there is the possibility that a shift in hormone balance may cause a change in the diffusibility of phosphatase.

2. The rise in alkaline serum phosphatase may indicate the response to increased injury. This is improbable because of the coincidental reduction of pain and decrease in acid phosphatase. However, in some patients metastases have spread in the absence of symptoms and with normal acid phosphatase. Therefore, the possibility of a temporary acceleration of bone injury cannot be dismissed entirely.

3. The shift in hormone balance following castration may stimulate the regenerative capacity of bone. Many investigators have shown that sex hormones may influence bone development although the mechanism remains obscure. While we have been unable to observe a close relationship between changes in alkaline serum phosphatase and variations of estrogen and androgen excretion, it must be remembered that androgen assays measure a number of different 17-ketosteroids which differ in their biologic activity. It is possible that after castration a shift takes place in the relative amounts of these steroid fractions and this may influence the regenerative capacity of bones. Therefore, a definite answer to this problem must await further work on the fractionation of the ketosteroids. It is significant that the alkaline phosphatase response to castration is usually different from that to stilbestrol therapy.

Huggins felt, as a result of his work with dogs, that the prostatic epithelium, whether normal or cancerous, was dependent for its growth on the relation of estrogenic to androgenic hormones in the blood. Estrogens were shown to decrease prostatic secretion, and androgens to increase it in experimental animals. The reason for castrating the man with prostatic cancer, according to this reasoning, was to remove the source of androgens. It has been known for several years that men excrete estrogenic hormones in their urine and since they have no ovaries, the adrenals have usually been thought of as the source of these substances. Since castration was not thought of as affecting the adrenals, the estrogens should remain constant thus bringing about a shift in estrogen-androgen ratio toward a higher estrogen and lower androgen level. Obviously, the administration of estrogens per se would bring about a similar sort of shift.

We were greatly surprised to find that these theoretical changes were not borne out by experimental observations in our laboratories. Twenty-seven cases of cancer of the prostate treated by castration were studied for their precastration levels of estrogen and androgen excretion. The estrogens averaged 16.6 mouse units per twenty-four hours and the androgens 6.1 mg. of androsterone equivalent as determined colorimetrically by the Callow modification of the Zimmerman meta-dinitrobenzene reaction. This is a low value for 17-ketosteroids, the healthy young male excreting 15 to 25 mg. in a similar period.

After castration, instead of estrogens remaining the same and androgens falling as we had expected, the estrogens dropped in all but one of 16 patients tested to a postoperative average of 8.5 mouse units, about one-half the precastration level, while the androgens determined colorimetrically tended to remain the same or rise slightly. The average change was from 6.1 to 7.1 mg. in the 17 patients tested. All postoperative levels were obtained one month or longer after castration. Gonadotropic hormones from the anterior pituitary were assayed before and after castration in 16 patients. Of these, there was a definite postcastration rise in 11, while 5 showed quantities of this hormone too low to measure either before or after castration. No case showed a fall in gonadotropic hormone in the urine postoperatively.

In contrast to these figures are those obtained by assays on 9 men before and after treatment with 2 to 5 mg. of diethylstilbestrol daily. The estrogenic assays on these men averaged 18.2 mg. per twenty-four hours before treatment. Following treatment this figure rose enormously because a certain amount of the diethylstilbestrol was excreted in the urine. The androgens (17-ketosteroids) before treatment averaged 8.9 mg. of androsterone equivalent per twenty-four hours, but after treatment these hormones fell in every case to an average of 5.4 mg. androsterone equivalent.

Of 6 patients studied for gonadotropic hormone excretion rate before and after stilbestrol, in none was there a post-treatment rise. Three showed no measurable excretion either before or after stilbestrol, while the other 3, showing small quantities of hormone in the urine before the administration of the drug, excreted too little to measure after it was started.

From the point of view of hormones excreted in the urine, therefore, the treatment of prostatic cancer by castration differs completely from treatment with diethylstilbestrol. Castration seems to cut estrogenic excretion in half, tends to raise 17-ketosteroid excretion, and to release the pituitary from testicular inhibition so that it pours out its gonadotropic hormone in excessive quantities. Stilbestrol raises the estrogenic excretion rate and decreases both the 17-ketosteroid excretion rate and the quantity of gonadotropic hormone in the urine. It appears that these two methods of treatment, while causing similar favorable clinical effects and the same changes in serum acid phosphatase, differ markedly in their effects on the hormones. These observations may explain why the patient who is having recurrent symptoms following castration is not improved by stilbestrol or the stilbestrol patient by castration, such treatment merely neutralizing the effect of the primary treatment rather than re-enforcing it.

Clarification of the true mechanism by which prostatic cancer regresses after castration or the administration of stilbestrol must await more detailed analysis of the changes produced. The Callow test, for in-

stance, measures all neutral steroids with a ketonic group in position 17 of which there are many. The apparent rise following castration may be in some inactive substance in this group and therefore the contrasting hormone changes between castration and stilbestrol administration may be more apparent than real. The clinical observation that one treatment does not aid a patient who relapses after having received the other is strong evidence, however, that these are opposite rather than similar forms of therapy.

SUMMARY

1. About 100 patients with cancer of the prostate have been treated at the Memorial Hospital either by castration or by the administration of stilbestrol given in doses of 1 to 5 mg. daily by mouth. Both forms of treatment have given striking clinical improvement, at least temporarily. Pain is abolished, appetite is increased, and a gain in weight results. These changes following castration are prompt. They occur more gradually with stilbestrol.

2. After an average of seven to eight months the patients are apt to have a return of pain and obvious progression of disease to death. Institution of other treatment, stilbestrol in the castrated patients or castration in the patients treated originally with stilbestrol, fails to affect the unfavorable course of the disease.

3. Some patients, following treatment, continue to remain clinically free from symptoms of prostatic cancer for long periods of time, two years or longer. The number of such prolonged arrests of cancer seems more frequent in the group treated with stilbestrol than by castration, so that this has become our routine initial form of treatment in the last eighteen months.

4. Stilbestrol seems to cause local regression in the size of the prostate and reduction in the amount of residual urine more frequently than castration.

5. Changes in bony metastases in general are toward an increase in calcification. Whether this represents healing of the lesions, a change in their properties, or a spread of tumor is hard to say. Occasionally an increase in roentgen density may be accompanied by the appearance of new shadows not previously visible.

6. Serum phosphatase determinations have proved useful for diagnosis and as a method of following the course of the disease. Elevation of serum acid phosphatase above 1 Bodansky unit is pathognomonic of prostatic cancer, although a low acid phosphatase does not rule out the presence of this disease. Serum alkaline phosphatase is usually elevated when bone metastases are present.

7. Serum acid phosphatase falls promptly in those patients who respond favorably to castration and rises again with a return of cancerous activity. The same changes occur more slowly in patients treated

with stilbestrol. Serum alkaline phosphatase often rises following castration and then slowly falls. The rise is not so apt to be present in patients treated with stilbestrol. The cause of this rise and subsequent fall is unknown. Reactivation of metastatic disease is usually reflected by a rise in serum alkaline phosphatase.

8. Castration decreases estrogenic excretion in the urine and usually causes a rise in androgens as measured colorimetrically as 17-ketosteroids by the Callow-Zimmerman test. It causes a rise in excretion of pituitary gonadotropic hormones in the urine.

The administration of stilbestrol decreases the output of the 17-ketosteroids and the gonadotropic hormone from the pituitary. After its administration the excretion of stilbestrol in the urine gives a marked rise in the estrogen assays.

Our findings suggest that the mechanism whereby castration and stilbestrol cause regression of prostatic cancers is fundamentally different.

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THE RELATIONSHIP OF HORMONES TO TESTICULAR TUMORS

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MALIGNANT testicular tumors are of tremendous interest both to the endocrinologist and to the oncologist for several reasons. They are a type of tumor which can be produced experimentally either by estrogenic hormones, as in mice, or by chemical irritants and natural or injected hormonal stimulation, as in fowls. Since the testis is one of the endocrine glands, tumors of this organ would be expected to, and as a matter of fact do, produce hormones. By assay of these substances it is often possible to test for the presence of active testicular cancer, even when it is not clinically obvious, and to venture a fairly shrewd guess as to the radiosensitivity of the tumor and the clinical course of the disease. Finally, the possibility of influencing tumors of one of the endocrine glands by administered hormones or changes in the hormone balance is an almost unexplored but fascinating field for the man interested in clinical research. There are several ways of causing atrophy of the normal testis. Will any of these affect the tumorous one?

HORMONES AND THE PRODUCTION OF TESTICULAR TUMORS

Teratomas of the testis have been produced successfully in roosters by several workers by the injection into the testis of zinc chloride or zinc sulfate, a procedure first carried out in 1925 by Michalowsky. Falin mentions a total of 23 so produced and in his latest articles adds 5 produced by zinc sulfate, 4 by zinc nitrate, and 1 by copper sulfate.

From the endocrinologic point of view the most interesting feature of these tumors is that all workers are agreed that the tumors occur only in the spring when zinc salts alone are given. Bagg, however, was able to produce 2 of his 6 tumors in the summer, one in July and the other in August, by continuous treatment of the fowls with extract of sheep anterior pituitary gland.

The tumors appear to be quite adult in type and resemble some of the so-called adult cystic teratomas seen in men. They are not transplantable and do not produce quantities of gonadotropic hormone sufficient to appear in assays of the blood. In this respect they are similar to their human counterparts.

The fundamental cause of these tumors seems to be the necrosis produced by the zinc or copper salts, although Falin thinks that zinc uniting with some of the protein material of the necrotic testis may form an

"inductor" or "evocator" similar to the "organizer" of Spemann. Bagg suggests a similar hypothesis. The role of hormones in the formation of these tumors seems to be secondary. No tumors have arisen from hormone stimulation alone, although Bagg treated a group of 22 birds in this way. However, the testis appears to be sensitive to the zinc only when it is actively growing under the influence of the host's own hormones in the spring or when stimulated by injected pituitary hormone.

A more direct relationship between tumor production and endocrine stimulation is seen in the testicular Leydig cell tumors of mice produced by prolonged treatment with estrogenic substances. These were described first by Bonser and Robson and by Hooker, Gardner and Pfeiffer. They have occurred only in the Strong A strain and in two other strains derived from it, but have been produced by three chemically different types of estrogens—estradiol benzoate, stilbestrol, and triphenylethylene. The sequence in their production seems to be an atrophy of the tubules and the formation of three different generations of Leydig cells. Tumors arise from the second or third generation. They are malignant and metastasize widely. Many appear to be functional, stimulating the seminal vesicles, an observation which suggests that they elaborate male hormone.

Leydig cell tumors in man are of great rarity, only 9 authentic cases having been reported. They appear to produce premature puberty when they occur in young boys, but no symptoms of an endocrine nature are described occurring in older men. We have seen 1 case recently occurring in an adult, and he had no gross sexual abnormalities or symptoms. Unfortunately, the nature of the tumor was not recognized until after it had been removed so that no assays for male hormone output could be carried out.

The precocious puberty in boys and the lack of symptoms in men would fit in with an overproduction of male hormone by this type of tumor, as is thought to occur in the mouse, for such an excess would be readily apparent in the undeveloped male but would probably show no effect in the adult male. There is no hint in the literature of a possible excess of estrogenic stimulation as the etiologic agent in the cases of this type of tumor in man.

There is some evidence from clinical observation that the more common teratoma of the testis in man also may have an endocrinologic etiology. For instance, it is a well-known fact that teratoma testis occurs much more frequently in men with undescended testicles than in the general male population. The incidence of cryptorchidism is given as 0.23 per cent in Army records, whereas 11 per cent of 7,000 recorded cases of cancer of the testis occurred in unilateral or bilateral cryptorchids. In a series of 203 cases of teratoma testis studied by us, 27 or 13.3 per cent were in men with cryptorchidism. That this high incidence is not related to trauma to the organ in the inguinal canal is

suggested by the figures of Gilbert and Hamilton who found 345 of 835 reported malignant testes to be intra-abdominal where they could not be readily damaged. Eleven per cent of these 345 occurred in pseudohermaphrodites, a finding that again suggests a hormonal etiology for the tumor.

Not all tumors occurring in patients with cryptorchidism arise in the undescended testicle. In Gilbert and Hamilton's series, 23 of 744 patients with unilateral cryptorchidism had the tumor in the normally descended organ. Six in our own series of 27 occurred in the normal testis. That this may happen more frequently than is shown by Gilbert and Hamilton's figures is suggested when it is considered that their data were taken from cases reported in the literature. It would seem probable that authors would be more apt to mention cryptorchidism when it affected the cancerous testicle than when it was found on the opposite side and appeared to have no direct connection with the tumor.

Another observation which points to a connection between hormones and the formation of teratomas in men is that these tumors, like those in the rooster, arise most frequently during the active sexual life of the patient. Unlike other forms of cancer, in which the peak in incidence is apt to fall after the age of 45, teratoma testis occurs in comparatively young men, the highest percentage lying in those between the ages of 35 and 39. If one compares the percentage of teratoma testis in the various age groups with the percentage of living males in the same age group, one finds more testicular cancers between the ages of 20 and 54 than one would expect were they distributed uniformly according to the number of males in each age group in the general population.

A third point of some interest in this connection lies in the finding of abnormal amounts of pituitary hormone in the urine of about 75 per cent of patients with teratoma, particularly of the unicellular or seminoma type. As has been shown by Hamburger and by our own experience, this hormone may be excreted in the urine in fairly large quantities without any clinical evidence of active testicular tumor being demonstrable. One may try to explain its presence as due to liberation of the pituitary from testicular control either because of destruction of one testis by tumor, roentgen therapy, or operative removal, but such an explanation does not account for the failure of the remaining testicle to suppress pituitary overactivity. Certainly the removal of one ovary in the female is not followed by the menopause. Why should the removal of one testicle have a different effect in the male?

Hamburger has shown this increased output of follicle-stimulating hormone from the pituitary to be accompanied by a decreased output of male hormone as tested on the comb of the capon. Is it possible that this shift in hormone balance with decrease in androgens and increase in pituitary gonadotropin is a primary condition which leads later to the formation of a malignant testicular tumor? It is obviously not possible

to answer such a question at present for no opportunity has arisen to observe a patient with such a hormonal change and to determine whether he later developed teratoma.

EXCRETION OF HORMONES BY MEN WITH TESTICULAR TUMORS

Gonadotropic Hormones.—That men suffering from testicular tumors may excrete large quantities of gonadotropic hormone was demonstrated by Zondek in 1929 and 1930, in 2 cases reported by him. It was confirmed the same year by Heidrich, Fels, and Mathias and later by Ferguson, Downes, Ellis, and Nicholson. Because the nature of the gonadotropic hormones was not well understood at first, certain errors have crept into the literature on the subject and have caused great confusion. Ferguson thought that there was only one hormone in urine from men with testicular tumors. This substance, in small quantities, caused the ripening of the Graafian follicles of the ovaries of infantile female rats or mice. When it was injected in five times the amount which gave follicle ripening, corpora lutea atretica were formed. Engle, and Evans and Simpson, among others, pointed out early that the gonadotropic hormone of pregnancy urine did not give the same reaction as extracts or implants of the anterior pituitary. However, Hamburger was probably the first to demonstrate clearly the differences in the reactions produced by pregnancy urine and urine from castrates or women past the menopause. Evans and his co-workers studied the type of hormone excreted by a patient with teratoma testis and came to the conclusion that it resembled that found in pregnancy urine in some respects and anterior pituitary extract in others. Fevold, Fiske, and Nathanson examined urine from another patient with chorioepithelioma testis and found it to give identical reactions in male and female rats, hypophysectomized rats, and male and female pigeons with pregnancy urine. Several other workers carried out similar tests (Fluhmann, Freed, and Main), but it remained for Hamburger to study a number of such patients and find that the type of hormone present was not constant. Some patients excreted chorionic gonadotropin as these investigators had said. Some, on the other hand, excreted the castrate type of gonadotropin, follicle-stimulating hormone, and some excreted a combination of the two.

As long as one thought of the hormone as of one type and produced by the tumor, it seemed logical to suppose that destruction of the tumor would result in disappearance of the hormone. Ferguson thought his material warranted such a conclusion, but later workers have found this hypothesis to be unreliable (Twombly, Temple, and Dean). Many tumors occur, metastasize, and kill the patient without showing any gonadotropic hormone at all in the urine.

It was noted by Ferguson that untreated tumors of approximately the same extent or with the same amount of metastases excreted varying

quantities of hormone. He explained this by saying that the amount of hormone excreted depended upon the type of tumor present and described very definite levels as characteristic of various histologic varieties. This also has proved only partially true. More extended study has shown a tendency for the more malignant embryonal adenocarcinomas and chorioepitheliomas to excrete large quantities of the chorionic type of gonadotropin; but many exceptions are found, widespread adenocarcinoma showing very little or no hormone, while some embryonal carcinomas (seminomas) show large amounts.

Hamburger, Bang, and Nielson also made an attempt to correlate gonadotropic hormone excretion with the histologic appearance of the tumor but laid the emphasis on the type of the hormone rather than the amount. They divided their cases into mixed epithelioma, seminoma, and polycystic teratoid mixed tumors, and maintained that the first was radioresistant and excreted the chorionic type of gonadotropin while the second and third excreted the castrate type, follicle-stimulating hormone. Seminomas excreting follicle-stimulating hormones were radiosensitive.

Hamburger admits that in 75 cases of testis tumor, he found 2 classified histologically as seminomas which nevertheless excreted large amounts, 1,000 and 50,000 M.U. per liter, of chorionic gonadotropin. These he labels pseudoseminoma; that is, they were tumors histologically of the unicellular type which behaved clinically and hormonologically like the mixed epithelioma type. He also lists 4 out of 21 mixed epitheliomas which excreted no hormone or only traces.

Recently Furuhjelm, studying the type of hormone excreted in 65 cases, has found this discrepancy also. Of 29 seminomas, 7 excreted no measurable hormone, 12 follicle-stimulating hormone, 5 chorionic gonadotropin, and 4 both types of gonadotropin. Of 7 malignant mixed epitheliomas, 6 excreted chorionic gonadotropin and one the castrate type of gonadotropin, follicle-stimulating hormone.

In our own laboratory, since 1936, we have attempted to distinguish the two types of hormone in all cases assayed. In these five and one-half years there have been 135 patients on whom complete clinical records are available. Of these, 65 are known to have had active tumor at the time at least one of the tests was run. Thirty-eight cases showed chorionic gonadotropin. Of these, 10 were reported by the pathologist as embryonal adenocarcinoma, and 7 as chorioepithelioma, tumors included under the name mixed epithelioma by Hamburger. Nine cases were embryonal carcinoma or embryonal carcinoma with lymphoid stroma (seminoma). In 7 there was no pathologic report. Two showed complete destruction of the tumor by x-ray before it was removed for pathologic study. Three cases showed mixtures of seminoma and embryonal adenocarcinoma.

Eighteen cases showed follicle-stimulating hormone only. Two of these were chorioepitheliomas, 7 were seminomas, 2 had no pathologic report, 3 were completely destroyed by x-ray before removal, 3 were adult cystic teratomas, and 1 was a mixture of seminoma and embryonal adenocarcinoma. No case of pure embryonal adenocarcinoma was found excreting the castrate type of gonadotropin only.

Finally, there were 7 cases in which no demonstrable gonadotropic hormone was excreted (below 50 to 100 M.U. per day). These included 1 case of embryonal adenocarcinoma, 2 seminomas, 1 with no pathologic report, and 3 showing complete x-ray destruction.

Our experience, then, confirms that of Furuhjelm—that one cannot tell surely the histologic type of the tumor by the type of gonadotropic hormone found in the urine. In this respect we disagree with Hamburger. However, in general all agree that the chorionic type of hormone is more typical of embryonal adenocarcinoma or chorioepithelioma (mixed epithelioma of Hamburger), while the castrate type of hormone is apt to be associated with seminoma (with frequent exceptions).

One point is worth noting in our material. That is that many of the 135 patients not included among the 65 known to have tumors when urinary tests were done were patients treated by orchiectomy elsewhere and sent to us for prophylactic irradiation of the lymph node drainage areas. Many of these showed the castrate type of hormone. Undoubtedly a number had active metastases from a seminoma which never appeared clinically because of the radiosensitivity of this tumor and its consequent destruction. In all probability the number of seminomas associated with the castrate type of hormone should be higher than our figures indicate.

When one examines the histologic preparations of these tumors, the types of tissue that one sees are so different that it is hard to free oneself of the idea that the chorionic type of hormone must be elaborated by one special type of tissue. The frequent association of high titers of this hormone noted by Hamburger, Furuhjelm, and us with embryonal adenocarcinoma suggests more than a chance occurrence. It is my own theory that the explanation for the discrepancies in which seminomas are associated with the pregnancy type of hormone is to be found in the fundamentally teratoid nature of all these tumors emphasized by Ewing. Four cases mentioned previously are of especial importance in this regard. These are the ones in which both types of tumor were found in the same testis. Often, the two types of tissue lay side by side in the same section, separated by only a thin fibrous septum. Testicular tumors are often large, and it is the accepted pathologic custom to take a few small representative sections from such a tumor in routine work. If the whole tumor were fixed and studied by large serial sections or many small sections, it is our belief that the correlation be-

tween the presence of chorionic gonadotropin in the urine and embryonal adenocarcinomatous tissue in the tumor would be much closer.

Prognostic Significance of Gonadotropic Hormones: Zondek pointed out in 1935 that any marked increase in excretion rate of prolan particularly of prolan B is an unfavorable sign and usually indicates metastases. The urine in 12 cases he studied showed corpus luteum formation in the test mice in 5, either with fresh urine or when concentrated. Three of these were dead when he wrote and the other 2 were not followed.

Hinman, who still fails to differentiate different types of gonadotropic hormones in teratoma urines, almost echoes Zondek in his latest article in which he says, "It is our experience that all of these patients with abnormal amounts of hormone in the urine have a poor prognosis and that most of them die of cancer within a year regardless of roentgenotherapy."

Hamburger makes a very clear distinction between the two types of hormone from the point of view of prognosis. He believes that the chorionic type is made by the tumor because this material has the same biologic properties as the hormone found in pregnancy urine which is thought to come from the placenta. A second argument for the origin of the hormone in the tumor is that there is a large amount of hormone in the tumor tissue and little or none in the pituitary gland. Finally, there seems to be a close relationship between the amount of hormone in the urine and the amount of active tumor tissue present in the patient's body. To this we might add a fourth observation: that we have never observed this type of hormone in male urine except when tumor tissue was known to be present or later proved to be so. Hamburger points out that the presence of this type of hormone is associated with a radioresistant type of tumor. "In all cases which have been under observation for a sufficiently long time, there have developed metastases, resistant to x-ray treatment, and all the patients died in a comparatively short time."

Furuhjelm agrees with this statement. In his own cases, 14 showed chorionic gonadotropin in the urine, of whom 6 were already dead at the time of his report, 4 living with metastases, and on 4 there was no note of their clinical condition.

We have found Hamburger's contention most correct in our own series of 135 cases. First, in no case was chorionic hormone present without active tumor. We believe with Hamburger that this hormone is a product of the tumor tissue itself and this is further evidenced by one patient who showed large amounts of hormone on his first test, which disappeared at once after orchiectomy. There have been 38 patients who showed this hormone and of these, 32 are dead. Four are still alive with active disease. The 2 remaining are alive and apparently free of disease. One is the patient mentioned previously, cured by simple orchiectomy;

the other has received a great deal of x-ray therapy and has stayed well for the three years preceding this report. The hormone in his urine has changed from small amounts of chorionic gonadotropin to moderate amounts of follicle-stimulating hormone.

Hamburger points out that the castrate type of hormone may be present with no evidence of active tumor and that it does not vary in amount with treatment of the tumor or extension of the cancer.

Again our experience is in complete agreement with this finding. In fact, it was the clinical observation of several patients who were excreting 1,000 M.U. of hormone per day, although they had been clinically free of cancer and without treatment for several years, which first drew our attention to the value of differentiating the types of gonadotropin.

Methods of Differentiating Gonadotropic Hormones of the Castrate From the Chorionic Type: Many different methods have been used to differentiate the different types of gonadotropin. The more practical ones are open to the objection that they use intact animals in which the action of the animal's own anterior pituitary may play a part. It has been pointed out by Hinman that only in hypophysectomized animals is this objection ruled out. If one gives castrate urine extract to a young hypophysectomized female rat, marked follicle ripening in the ovaries is brought about. Chorionic gonadotropin, on the other hand, causes merely a luteinization of the theca cells and, at least in small doses, no follicle formation. Such animals have been used in testing a few individual urines from patients with testicular tumors (Fluhmann, Fevold, and others). These have been patients excreting chorionic gonadotropin in large quantities. No investigator has used hypophysectomized animals routinely because of the difficulty in obtaining such test animals in any quantity.

Various types of birds may offer means of differentiating gonadotropic hormones. For instance, the common English sparrow in the eclipse plumage of the fall and winter responds by blackening of the bill to pituitary hormones but shows no such reaction to pregnancy urine. Male African weaver birds show blackening of the white breast feathers on injection with luteinizing hormone from the pituitary but not from follicle-stimulating hormone. Hamburger has used infantile cocks very successfully in differentiating hypophyseal from chorionic hormone. Again Lahr, Riddle, and Bates have shown increase in the weight of the testis in doves or the ovaries of pigeons from pregnant mare serum or anterior pituitary extract, an effect not produced by pregnancy urine.

Fevold has reported quantitative extraction of chorionic gonadotropin by tricresol, and destruction of the follicle-stimulating hormone of castrate urine by the same process.

The most practical method of differentiating the hormones is by the use of infantile female rats and mice. In these animals there are a number of differences which allow one to tell which hormone has been

injected. The most obvious and easiest is the difference in the morphology of the ovary itself and for this purpose mice are superior to rats since little spontaneous ripening occurs in animals under 9 Gm. in weight. Pregnancy urine given in dilutions just strong enough to give a positive reaction will cause the maturation of one or two large Graafian follicles. Along with this one sees a ballooning of the uterus with watery fluid. Larger doses result in the formation of one or many corpora lutea atretica. Sometimes this reaction is accompanied by Zondek's reaction II, the formation of corpora hemorrhagica.

Castrate urine, on the other hand, causes the ripening of many or all the follicles present. Either no corpora lutea are formed or only with very high dosage. While in borderline cases it may be hard to distinguish the two types of reactions, when one has looked at a few examples of each, it is surprisingly easy to distinguish them in most instances. This is particularly true if sets of ovaries from animals injected at different levels are available for histologic study. The uteri of animals injected with castrate or menopausal urine are hypertrophied but not dilated.

A few cases have been described in which the urinary gonadotropin resembled that found in pregnant mare serum. The presence of this type of hormone is characterized by the typical picture in the ovary produced by castrate urine when a small dose is given. However, when slightly larger doses are given, multiple corpora lutea appear. That this gonadotropin is a mixture of the chorionic with the castrate type, and not identical with pregnant mare serum hormone, has been demonstrated by injecting it into rabbits. Mare serum hormone so treated is either destroyed or excreted in very small amounts. The substance produced by these rare cases of testicular tumor was excreted in amounts of 20 per cent of the injected total.

Chorionic gonadotropin may be distinguished from follicle-stimulating hormone in another way. If increasing doses of pregnancy urine are given to infantile female rats 26 to 28 days old and the ovaries weighed after 100 hours, the ovarian weights will be found to increase very slowly until doses in the neighborhood of 10,000 times the minimal effective dose are reached, when there will be a sharp rise. Castrate or menopausal urine gives a sharp, prompt rise to maximal weights with doses of only two to four times the minimal effective dose. Many urines from teratoma of the testis have been studied in this way by constructing dose response curves with infantile female rats. In all cases those showing the chorionic type of follicle ripening and corpus luteum formation have given curves identical with pregnancy urine gonadotropin, while those showing follicle-stimulating hormone by mouse ovarian morphology have given the menopausal type of rat ovarian dose response curve.

There is another differentiating reaction between the two types of hormones in human urine, and that is the relative sensitivity of the rat

and the mouse to each. When chorionic gonadotropin is present in the urine, the infantile female rat is about five times more sensitive than the infantile mouse, whereas the production of estrus with follicle-stimulating hormone from castrate or menopausal urine requires two to three times more hormone in the case of the rat than in the mouse. This last reaction has been used very little to distinguish these substances from one another.

In our own laboratory we have confined our efforts in distinguishing the hormones to the morphologic differences they produce in the ovaries of infantile female mice, 21 days old, weighing 7.5 to 9 Gm. These animals are injected in lots of 6, each animal receiving a different quantity of fresh urine or alcohol concentrate as follows: Three are injected with 0.1, 0.2, or 0.4 c.c. of fresh urine on each of five occasions within forty-eight hours. The other 3 receive similar amounts of a ×5 alcoholic concentrate. This is made by precipitating 40 c.c. of urine with 200 c.c. of 95 per cent ethyl alcohol, collecting the precipitate, washing twice with ether, drying, and redissolving in 8 c.c. of water. The animals are killed at 96 to 100 hours and the ovaries examined grossly for follicles and corpora lutea. If either are found in any animal, groups of 5 mice are injected with the lowest quantity producing the original reaction, one-half this amount, and double the amount. That is, the reaction is checked on groups of 5 animals at, above, and below the original test dose. The ovaries of this set of animals are fixed, sectioned, stained, and studied under the microscope. We have noticed that the formation of corpora hemorrhagica occurs only in the ovaries of animals injected with urine containing the chorionic type of gonadotropin, at least in our experience.

EXCRETION OF ESTROGENS BY MEN WITH TESTICULAR TUMORS

Hamburger investigated the estrogenic excretion rate of 23 men with testicular tumors. Of these, 10 had seminoma, of whom 9 showed normal rates and 1 a slightly increased amount. One pseudoseminoma showed increased amounts of chorionic gonadotropin and slightly elevated estrogenic excretion. Of 8 mixed epitheliomas, 1 showed no estrogens, 2 were normal, 3 moderately elevated, and 2 markedly elevated. There was a direct correlation between the amount of chorionic gonadotropin and the increase in total urinary estrogen excretion. The 3 highest estrogenic values were in urines containing more than 100,000 M.U. of chorionic hormone per day.

In our own laboratory only one patient has been studied for his estrogenic excretion rate. This man had a widespread chorioepithelioma, arising in the testis, with well-marked gynecomastia. He showed very marked elevation of urinary estrogens over normal men.

The suggestion immediately presents itself that the tumor itself is responsible for the production of estrogens as well as gonadotropin and that the increased estrogen titers are directly related to the gynecomastia

seen in cases with widespread active disease. However, there seems to be another type of gynecomastia which occurs in patients with no evidence of humor, possibly as a hemicastration effect. Gynecomastia has often been thought a bad prognostic sign, and this is undoubtedly true when it is associated with high chorionic gonadotropin, but in 6 of the 12 cases observed by us, there was no such correlation and the patients did well.

In contrast to our own findings and those of Hamburger are those of Smith and Smith, who found low urinary estrin levels in 4 cases of chorioepithelioma, 3 in men and 1 in a woman.

EXCRETION OF PROGESTERONE BY MEN WITH TESTICULAR TUMORS

As far as we are aware, the only patient studied for this possible excretion of progesterone or its metabolic product, pregnandiol, is one seen in our own laboratory. This man, with a chorioepithelioma of the testis, was found to excrete from 10.5 to 16.5 mg. per forty-eight hours of a substance identified by its melting point and mixed melting points as probably free pregnandiol.

EXCRETION OF ANDROGENS BY MEN WITH TESTICULAR TUMORS

Because he found no evidence of a decreased estrogenic excretion rate which might account for the increased output of the castrate type of gonadotropin in 75 per cent of the patients with seminoma, Hamburger sought for a decreased testicular function as determined by a decreased male hormone excretion in the urine. In this he was successful. Of 19 cases of seminoma in which urine was assayed by direct application of a urinary extract to the combs of white Leghorn capons, 15 showed a moderate to marked decrease in total biologically active androgens. The average excretion rate for all 19 was 10 I.U. per day as compared with 50 I.U. for normal young and middle-aged men without tumors. Twelve other men with tumors causing the excretion of chorionic gonadotropin were tested, of whom one-half had normal androgenic values. The other 6 were below normal. He suggests that the formation of a large quantity of chorionic gonadotropin may stimulate the other testis or the adrenals to the production of male hormones and so explain the difference in output between the two types of tumors. Hamburger thinks the low output of male hormone is due to damage or removal of the affeteed testis, and that this in turn releases the pituitary which puts out the increased amounts of follicle-stimulating hormone found in the urine. As pointed out in the early part of this article, one may consider these changes as the cause rather than the result of the tumor.

In the case previously referred to and assayed for male hormone by the colorimetric method of Callow, a high normal (24 mg. androsterone equivalent per 24 hours) was found while the biologic activity of this material tested on the chick comb was low (3.1 mg. androsterone equivalent per 24 hours, 31 I.U.—normal = 20 to 100, average 50 I.U.).

THE TREATMENT OF TESTICULAR TUMORS WITH HORMONES

As far as we are aware, our own have been the only efforts along this line of therapeutic endeavor. The first possibility that presented itself was the administration of an antigonadotropic hormone. We were supplied* with some highly potent antigonadotropic goat sera. These were administered to 2 patients with high titers of chorionic gonadotropin in the urine, in the expectation that the amount of hormone would fall. Instead, it rose.

Similar attempts were made with pregnancy and placental blood sera in another case, since several authors believed this fluid to contain substances antagonistic to the growth of chorionic tissue. Again there was a rise in hormone titer, and it was possible to show that this rise and that observed with goat serum were both probably nonspecific serum reactions.

Lately, Huggins' work on cancer of the prostate has awakened the hope that changes in hormone balance may give regressions in cancers of endocrine-controlled organs. Large doses of estrogens in animals produce testicular atrophy. Will they do anything to testicular tumors? So far we have tried it on 2 patients without any clear-cut success, but in neither case was the administration continued long enough. The possibility still remains that this or some similar form of therapy may be effective.

SUMMARY

1. Teratoma testis has been produced in the fowl by the injection of zinc or copper salts when the testis was simultaneously stimulated by the animal's own or injected hormones.

2. Leydig cell tumors have been produced in mice with estrogens.

3. Certain facts about teratoma testis cases in man suggest an endocrine etiology. These are the frequent occurrence of teratoma in patients suffering from cryptorchidism or pseudohermaphroditism, occasionally in the descended testicle, the high incidence of this type of tumor during the period of greatest sexual activity, and the finding of high levels of the castrate type of gonadotropin, follicle-stimulating hormone, and low levels of androgenic hormones in the urine of patients with testicular cancer, particularly seminoma. These last-mentioned changes do not appear to be dependent upon the presence or absence of active tumor.

4. The gonadotropic hormone found in the urine of men with testicular tumors appears to be of two kinds, chorionic gonadotropin identical with the gonadotropin of pregnancy urine, and follicle-stimulating hormone similar to that found in castrate or menopausal urine.

5. Chorionic gonadotropic hormone is found in the urine only when active tumor tissue is present. It is associated with all varieties of

*Through the kindness of Dr. A. S. Parkes.

teratoma, but certain observations suggest that it may be produced by the tissue spoken of as embryonal adenocarcinoma and that when it appears in cases of seminoma, this is a further proof of the essential teratoid nature of all such tumors. It is likely that the other type of tissue would be found to be present were a thorough search of all cancerous tissue present in the body to be made.

6. The presence of chorionic gonadotropin in the urine usually means that the tumor will be radioresistant and the patient will die in a short time. Thirty-two of 38 such patients in our own series are dead. Four are living with metastases. Only 2 are apparently cured.

7. Chorionic gonadotropin can be distinguished from follicle-stimulating hormone by its action on the ovaries of hypophysectomized female rats, by its failure to act in certain birds, by its different properties when mixed with tricresol, and by the difference in histologic picture and in ovarian weight when it is injected into infantile female rats or mice. From a practical laboratory point of view, the two hormones are most easily distinguished by the differences in the histologic appearances of infantile mouse ovaries when the animals have been injected with fresh or concentrated urine.

8. Those teratomas which produce large quantities of chorionic gonadotropin also seem to excrete abnormally high levels of estrogens. They may excrete pregnandiol.

9. Teratomas of the testis, especially those classified as seminomas, are apt to show very low levels of biologically active androgenic hormones in the urine.

10. The testicular tumors would seem to offer a tempting field for possible therapy by hormone administration.

ADRENAL CORTICAL TUMORS—PHYSIOLOGIC CONSIDERATIONS

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INTRODUCTION

THE student attempting a systematic exposition of the means by which adrenal cortical tumors disorganize the physiologic economy of their hosts is thinking and often guessing well before his proper time. The data he must deal with are still fragmentary and often incongruous. His dubious recompense lies in the circumstance that he may cherish his favorite speculation for a long while before yielding to the hard, new, incontrovertible fact.

For a generation or more the arresting transformations of the human body induced by the secretions of these tumors have been known in some detail and have transcended experimental experience. It had never been possible until recently to secure an adrenal agent of such purity and potency that its effects in heavy, protracted dosage in animal and man could be compared with the phenomena seen in patients. Indeed large amounts of life-sustaining adrenal extracts were so well borne by animals that little support accrued to any notion that excessive amounts of normal adrenal "hormone" would prove disadvantageous. Furthermore, it was never possible to contrast suprarenal failure as seen in Addison's disease with presumed hyperadrenal states in a sufficiently clear and uncomplicated fashion. The diversity and the bizarre character of the defects in the victims of adrenal tumors were far too great. Accordingly, no theory conceiving of one as due to the deficiency of a single hormone and the others as due solely to the excess of that same hormone has been seriously entertained. The clinical expressions of adrenal hyperfunction remained mysterious phenomena beyond experimental realization and at the limits of speculative grasp.

During recent years, however, progress in steroid chemistry has permitted the isolation of a multitude of compounds from the adrenal cortex, the chemical characterization of many, and the partial synthesis of a few. The physiologic properties of these substances are often so different that it has seemed hardly likely that any one of them can represent *the* adrenal hormone.[1, 2] In any event, the mere presence of numerous compounds with various propensities introduces the possibility that each may contribute in its own special manner if discharged to the

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organism by a tumor. Familial relationships between adrenal cortical steroids and those from the gonads, indeed the presence of several sex hormones in the adrenal cortex, have served to make the intermixture of sexual and nonsexual symptoms in adrenal disorders more comprehensible. The way is now open for the systematic study of the effects of excessive amounts of adrenal derivatives with the expectation that many of the manifestations of adrenal tumors can be reproduced with acceptable verisimilitude and with justice to the variety of disease.

I intend to outline this pattern of contemporary research bearing upon adrenal hyperfunction, and to interpret the signs and symptoms of the victims of adrenal cortical neoplasia in terms of the properties of adrenal steroids and their chemical relatives in so far as I can. Such interpretations will inevitably be tentative, clumsy, and often erroneous, as much decisive work lies in the future.

THE NATURE OF THE COMPOUNDS ISOLATED FROM THE ADRENAL CORTEX

The greater part of our knowledge of the chemical nature of the steroids obtained from the adrenal gland is due to the work of Reichstein and his associates in Switzerland; Kendall, Mason, Wintersteiner, Pfiffner and their associates in this country and Beall in England. These developments have been fully treated in the reviews of Reichstein and Shoppee[2] and Pfiffner.[3] These and several accounts by Kendall[1, 4-6] give much detail concerning the relationships between chemical structure and biologic response. Long's review[7] is especially valuable for its analysis of the effects of cortical compounds on carbohydrate and protein metabolism, and his article with Katzin and Fry[8] for an analysis of the comparative roles of the adrenal cortex and the hypophysis in carbohydrate metabolism. Ingle's review,[9] chiefly of biologic response in general, is well designed to stress many of the infinite number of incompletely answered questions in adrenal physiology. These accounts will be drawn on heavily in the following.

Twenty-eight steroids have now been isolated from the adrenal gland and the structure of all but one determined with considerable certainty.[2] The majority of these, including all possessing properties in any way distinctive of adrenal cortical function, share the 21-carbon skeleton typified by allo-pregnane (I) or δ-4 pregnene (II). Biologic activity of adrenal character has been most clearly ascribed to those members of the latter series bearing a ketonic group at carbon 3. By virtue of the side chain attached to carbon 17 the compounds with properties distinctive of the adrenal cortex are closely related to progesterone (III), and differ thereby from the typical androgens and estrogens, as illustrated by testosterone (IV) and estrone (V). Indeed, progesterone itself has been found in the adrenal and bears an intimate functional relationship to the more characteristic adrenal steroids in that it will, unlike either androgens or estrogens, protect both rat and ferret against death after

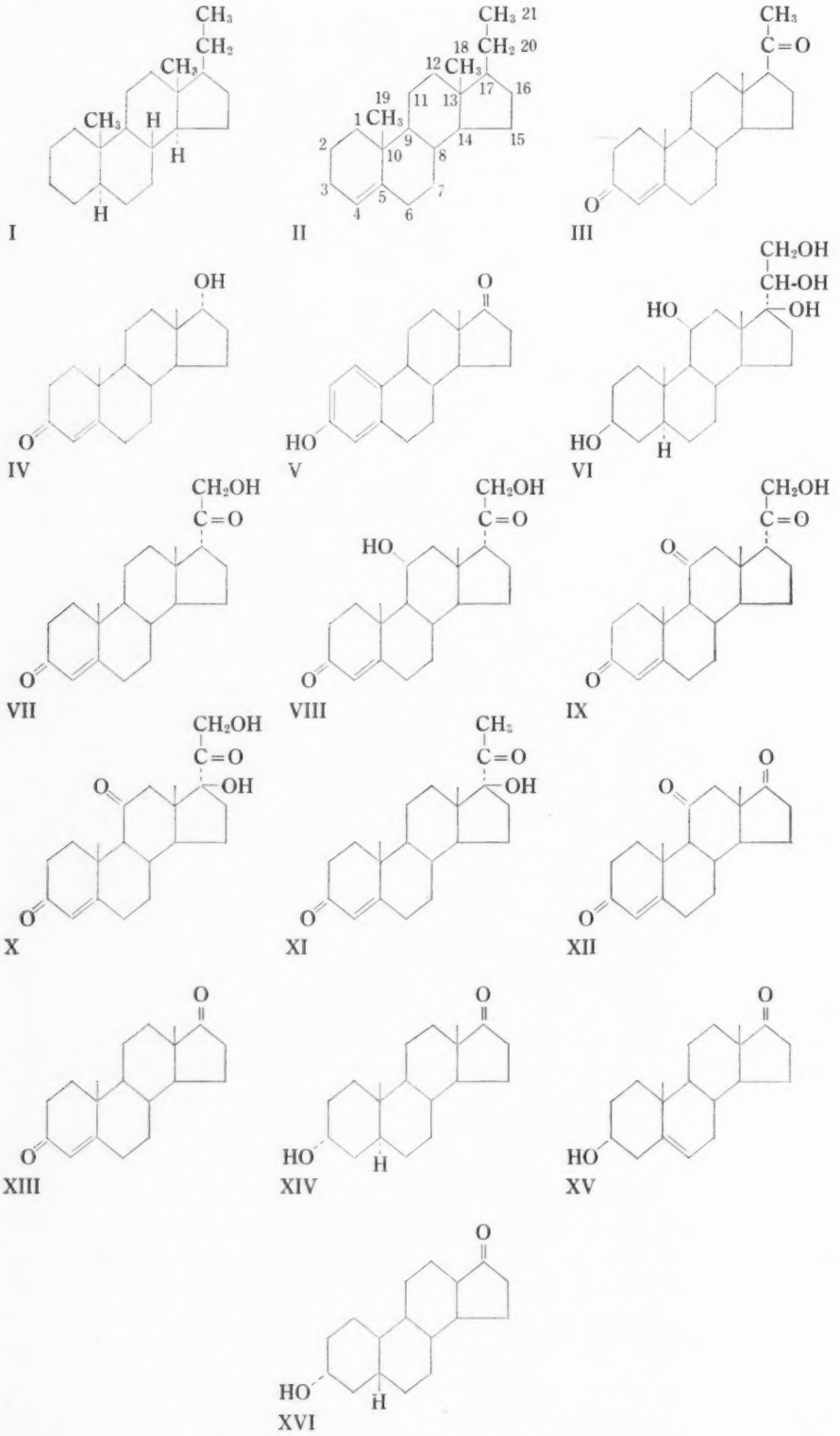

Fig. 1.—(*For legend see opposite page.*)

adrenalectomy when given in sufficient dosage. No place for progesterone as an adrenal secretion, however, has as yet been found. The remainder of the adrenal steroids capable of repairing suprarenal insufficiency in the ordinary sense seem devoid of progestational, androgenic, or estrogenic properties to a material, functionally significant degree as far as is now known. Instances exist, as in the progestational effects of large amounts of desoxycorticosterone, in which a typical gonadal influence may be simulated. Such reactions may require consideration in some future interpretation of the response to large amounts of secretion delivered by neoplasms. For the time being they have not entered into physiologic calculations. Certain other influences of the steroid hormones, notably the induction of sodium, chloride and water retention, and the depression of thymic growth, are shared, at least to some extent, by gonadal and typical adrenal steroids and do require detailed assessment in the interpretation of normal processes. They represent physiologic reflections of the chemical consanguinity between adrenal and gonadal hormones.

Most of the compounds isolated from the adrenal cortex have been assayed by some test indicative of adrenal insufficiency. By such tests, several of the pure steroids, as for example, allo-pregnane 3β 11β 17β 20 (?) 21 pentol (VI), have been inactive. The review of Reichstein and Shoppee describes these compounds in detail. For the present, one is disposed to regard them as progenitors or derivatives of the true adrenal secretions, seeking roles for them somewhere in the intrinsic metabolism of the gland itself. As will appear subsequently, however, many phenomena appear in the victims of adrenal tumors which are not as yet fully accounted for by properties of the adrenal steroids now deemed biologically active. Further examination of the supposedly inert compounds in the light of such phenomena must be undertaken.

Desoxycorticosterone (VII) which differs from progesterone (III) only in the presence of an alcohol group at carbon 21, has been isolated from the adrenal itself,[2] but appears to be present in such small amounts as to be often undetectable.[4] This fact while creating a presumption against its being a hormone is not conclusive. The partial synthesis of this compound by Steiger and Reichstein has made it available for physiologic and clinical study in adequate amounts. It is used, thus,

Fig. 1.—Adrenal steroids and related compounds. Enumeration of the carbon atoms given for II, δ-4 pregnene. Stereoisomerism indicated by dotted or straight lines according to the conventions discussed by Reichstein and Shoppee. The attached methyl groups are given only for I and II. Otherwise, point of attachment is indicated by straight lines at the junction of two rings.

I	Allo-pregnane	IX	Dehydrocorticosterone
II	δ-4 pregnene	X	17-hydroxy-11-dehydrocorticosterone
III	Progesterone	XI	17β hydroxyprogesterone
IV	Testosterone	XII	Adrenosterone
V	Estrone	XIII	Androstenedione
VI	Allo-pregnane 3β 11β 17β 20 (?) 21 pentol	XIV	Androsterone
		XV	Dehydroisoandrosterone
VII	Desoxycorticosterone	XVI	Etiocholan 3α ol 17 one
VIII	Corticosterone		

largely as the acetate. Its most dramatic effects are upon electrolyte and water metabolism. It corrects the urinary loss of sodium, chloride, and water and the retention of potassium, characteristic of suprarenal insufficiency in several species.[10, 11] While such renal influences are readily measured and are of great importance to the organism, less well-defined modifications of the internal distribution of these electrolytes and water are not to be ignored. Since perversions of electrolyte and water metabolism are fatal to most animals whose salt intake is limited and who are not otherwise subjected to special stress, desoxycorticosterone or its acetate is most effective in maintaining the lives and apparent health of such animals. Indeed, Kendall estimates that as little as 15 micrograms per kilogram per day will suffice for the adrenalectomized dog. Thorn and his co-workers[12] find that patients with Addison's disease may need from 1 to more than 10 mg. of the acetate per day when injected intramuscularly in sesame oil, the vast majority requiring from 1 to 5 mg. per day. Only 60 per cent of this amount is necessary when the steroid is absorbed more slowly from subcutaneous crystalline implants. In contrast to this, corticosterone (VIII) is required by the dog in amounts of approximately 100 micrograms per kilogram per day and is distinctly less effective than desoxycorticosterone acetate in reducing urinary sodium and chloride excretion in man.[13] The feebler effects of corticosterone and dehydrocorticosterone (IX) on electrolyte excretion are qualtitatively like those of desoxycorticosterone, however.[10] It should be mentioned that little experience with esters of corticosterone has been acquired.

Despite its efficiency in maintaining the lives of adrenalectomized animals under the protection of the laboratory, desoxycorticosterone fails when certain specific stresses are placed upon the organism. Among the best understood of these stresses are those that bring out defects in carbohydrate metabolism which are imperfectly realized in the protected state. Several steroids obtained from the adrenal gland and having in common an oxygen atom on carbon 11 will efficiently correct these defects in carbohydrate metabolism. These compounds, corticosterone (VIII), dehydrocorticosterone (IX), 17-hydroxycorticosterone (X), and 17-hydroxy-11-dehydrocorticosterone (X) are commonly identified in this country by letters given them in Kendall's laboratory. In this sequence these are B,A,F, and E. Reichstein's lettering[2] differs and should not be confused with that of Kendall. As judged by isolation procedures which, of course, may err, A and E are most abundant in the gland (340 and 330 mg. per 1000 pounds respectively) while B (180 mg.) and F (less than 100 mg.) are less abundant, according to Kendall.[4] Resembling desoxycorticosterone in the presence of ketones at carbon 3 and carbon 20, a double bond at 4 to 5, and an alcohol group at 21, these four substances all differ from it in the presence of the oxygen at carbon 11. This feature has thus far seemed to be

decisive for influence upon carbohydrate metabolism and to have retarded the synthesis of these steroids.

The steroids influencing carbohydrate metabolism appear to do so by increasing the rate of gluconeogenesis from protein and other percursors when this is necessary and by influencing the rate of disposal of glucose.[7] The relative importance of these two processes varies with experimental conditions. Much is obscure concerning the precise site of action of these substances and the extent to which fat metabolism is involved. In any event the depletion of glycogen stores and appearance of hypoglycemia during fasting in the adrenalectomized animal are prevented, the equisite sensitivity to insulin is abolished, and phlorhizin and pancreatic diabetes are permitted their conventional evolution. The fatigability of electrically excited muscle in Ingle's test procedure is made more nearly normal in the adrenalectomized rat by the intravenous infusion of glucose or by steroids with an oxygen on carbon 11. In the prevention of vascular collapse induced by intestinal manipulation as described by Swingle and his associates,[14] the favorable effect of 11-oxygen compounds may depend more upon obscure benefits accruing to the intrinsic metabolism of the vascular system than upon the availability of circulating glucose. Similar situations may well exist elsewhere. In none of these instances does desoxycorticosterone seem to repair the defect due to adrenalectomy. In so far as the limited supply of the proper cortical steroids has permitted study in man, the data of Thorn and his associates,[15] using cortical extract, corticosterone, and 17-hydroxy-11-dehydrocorticosterone to correct anomalies of carbohydrate metabolism in Addison's disease, are consonant with work in lower forms. Corticosterone is a relatively weak agent, the effects of 85 mg. being much less clear cut than those of 33 mg. of 17 hydroxy-11-dehydrocorticosterone.

Thorn and Clinton[16] later provided a more complete analysis of the effects of 33 mg. of 17 hydroxy-11-dehydrocorticosterone (compound E) in a patient with both Addison's disease and diabetes mellitus, a patient who interestingly enough could maintain a higher blood sugar level than is customary in adrenalectomized depancreatized animals. Under the influence of compound E the urinary glucose was doubled, while urinary nitrogen, phosphorus, sodium and chloride, and urine volume were increased. Urinary potassium was unaffected. The blood sugar was raised, and the basal metabolic rate somewhat increased, while the nonprotein respiratory quotient was reduced from 0.82 to 0.73. Ketonuria was increased. The increase in protein decomposition as judged by the rise in urinary nitrogen was insufficient to account for more than a small fraction of the glucose excreted, just as in several previous experiments in lower forms.[7, 17] The interpretation offered, in agreement with previous workers, is that glucose consumption relative to that of fat was reduced. The entire problem of the interconversion of glucose

and fat under these circumstances and of the discriminative utilization of these two sources of energy by the body is worthy of further study.

The disposition of certain doses of 17-hydroxy-11-dehydrocorticosterone to increase urinary sodium and chloride excretion as illustrated, is shared by 17-hydroxycorticosterone[18] and differentiates these substances bearing a hydroxyl at carbon 17 from their relatives dehydrocorticosterone and corticosterone, which always induce sodium and chloride retention when given in effective dosage.[10] The renal loss of phosphorus after compound E is attributable to the loss of tissue in the course of gluconeogenesis from protein and has been observed repeatedly in rats[7, 17] and dogs,[19] with steroids exerting this effect. The absence of potassium diuresis either in a human subject or in dogs,[19] in brief experiments, when such tissue loss prevails, may be due to temporary transfer of potassium to sites of new glycogen deposit. In the experience of Long,[7] in the rat, potassium was lost with phosphorus and nitrogen during gluconeogenesis induced by any adrenal agent. Desoxycorticosterone acetate is devoid of influence on either nitrogen or phosphorus excretion save in recovery from suprarenal insufficiency when material retained in the body during a period of renal failure is discharged.

The induction of atrophy of the normal adrenal cortex may apparently be produced by nearly any of the biologically active adrenal steroids,[20-22] although desoxycorticosterone is less potent than corticosterone or 17-hydroxy-11-dehydrocorticosterone in either regard.[21, 22] The thymus was well preserved in rats receiving 5 mg. of desoxycorticosterone acetate daily for four weeks in one series of experiments.[23] Corticosterone and 17-hydroxy-11-dehydrocorticosterone readily induce thymic atrophy.[21, 22]

The potency and the properties of certain adrenal extracts are not as yet fully accounted for by the pure steroids contained therein. These possibilities exist: (1) Some unknown steroid is present; (2) some known steroid exists in such a form, for example as a conjugate, that its activity is enhanced in some respects and reduced in others; (3) some obscure synergism between two or more known compounds is operative. Potent amorphous fractions have been obtained by several workers. That of Kendall[4] will maintain adrenalectomized dogs in good health with normal blood concentrations of urea and electrolytes in a dosage of 1 to 2 micrograms per kilogram per day. For comparable effects 15 micrograms of desoxycorticosterone acetate per kilogram, 100 micrograms of corticosterone per kilogram, and 10 mg. of compound E per dog are required. Kendall, furthermore, ascribes an especial advantage to this fraction in maintaining renal function as judged by blood urea concentration. The amorphous fraction does not effect carbohydrate metabolism nor induce adrenal and thymic atrophy readily as do the substances with oxygen at carbon 11, nor does it distort the pattern of serum electrolytes when given in large dosage as does desoxy-

corticosterone. An elucidation of its nature is essential for our understanding of adrenal secretions.

Of the remaining 21 carbon atom steroids isolated from the adrenal cortex, 17-hydroxy-desoxycorticosterone possesses some biologic activity analogous to that of desoxycorticosterone, while 17β hydroxyprogesterone (XI) is a weak androgen which lacks progestational and typical adrenal cortical functions. Neither, however, has been fully characterized in metabolic studies. Of the 19-carbon atom steroids, adrenosterone (XII), adrostane-3 (β):11 (β) diol-17-one, and δ-4-androstene: 3-17 dione (XIII) are androgens, although not strongly so, and may arise during the working up of the extracts. Great interest attaches to the androgenic compounds in view of the possibility that the normal adrenal cortex of man may have some effects related to those of the androgens and that hyperplastic and neoplastic adrenal cortices certainly do. Powerful androgens such as testosterone have not as yet been obtained from the adrenals. Estrone (V) has been obtained from the adrenal. The significance of this finding is enhanced by the occasional occurrence of estrogen-secreting neoplasms in mice and man.

The biologic effects of large amounts of the various steroids of the adrenal gland will be discussed in conjunction with the interpretation of the manifestations of adrenal cortical tumors. Numerous less well-studied physiologic expressions of adrenal function, such as resistance to cold, to water intoxication, and to thyroxin and cutaneous pigmentation have been omitted from the discussion since it is not yet known that agents different from those described are required for their control.

THE NATURE OF THE ADRENAL CORTICAL HORMONES

The disposition to refer to any of a multitude of compounds which are obtained from a gland or which, when synthesized, possess biologic properties resembling those of some internal secretion as a hormone should be recognized for what it is, a convenience which taken too seriously begs an important scientific question. Short of the utopian accomplishment of isolating a humoral agent from the blood stream without impairing its integrity, we lack direct means of ascertaining what is and what is not the actual secretion of a gland. As Houssay[24] has recently emphasized with regard to the pituitary body, even the most thorough and brilliant of chemical analyses of the constituents of a tissue must be supplemented by physiologic analysis. Precision of replacement therapy is necessary for a reliable inference as to what is delivered to the circulation by a gland of internal secretion. The enormity of this task as far as the adrenal cortex is concerned is readily apparent, the biologically active constituents of the gland are numerous and varied, the functions subserved by the gland are complex and widely ramifying. Even a steady determination to seek unity in the midst of

prolixity, such as is apparent for example in the thinking of C. N. H. Long[7] or Fuller Albright[25] has its frustrations.

Of the adrenal steroids isolated, corticosterone seems most nearly to fulfill the physiologic requirements imposed upon any agent offered as a prospective sole and single secretion. It possesses both a capacity to sustain the adrenalectomized animal living on a normal supply of salt and a capacity to initiate the necessary modifications of carbohydrate and protein metabolism required by the adrenalectomized animal called upon to endure pertinent metabolic stress. That it is less effective than desoxycorticosterone in the former regard and than 17-hydroxy-11-dehydrocorticosterone in the latter may not be decisive. Greater potency may possibly be obtained from thus far unstudied esters, illustrated by the superiority of desoxycorticosterone acetate to desoxycorticosterone, and the type of conjugate provided by the gland itself may be expected to have advantages. There is no reason to believe that corticosterone could ever be androgenic. This limitation probably exists, however, for any and every agent serving to repair suprarenal insufficiency and lends significance to anatomic studies seeking to implicate special cell types in androgen secretion.

The most important physiologic evidence casting doubt on corticosterone as the sole secretion with typical adrenal properties seems to lie in the work of Lewis and his associates.[19] The urinary excretion of sodium and chloride as well as of nitrogen and phosphorus was increased in the normal dog exposed to anoxia as compared to the adrenalectomized dog. Such accompaniments of gluconeogenesis evoked by this procedure are unlike any known effects of corticosterone and suggest the direct participation of a compound like 17-hydroxy-11-dehydrocorticosterone in the process to effect sodium and chloride loss. On the other hand these very properties of 17-hydroxyl compounds would seem to unfit them as agents for conserving body salt. In this connection, however, the experience of Kendall in maintaining adrenalectomized dogs with 10 mg. of compound E daily, and of Kuizenga and Cartland,[26] in maintaining adrenalectomized rats with compound E, demonstrates that dosages of the 17-hydroxyl compounds may be found which are not inimical to the maintenance of salt and water balance.

It will be of great interest to examine the new pure pituitary adrenotropic principle[27-30] for its effect on salt and water metabolism. As thus far studied this agent evokes a gluconeogenic, thymus-depressing, adrenal secretion, which antagonizes insulin and whose catabolic properties oppose the effects of the growth hormone of the pituitary body.[31] These are the responses expected of potent adrenal steroids bearing an oxygen on carbon 11. It is problematical whether such an adrenal hormone evoked by such an adrenotropin could efficiently conserve body salt in the manner of desoxycorticosterone or corticosterone. It should furthermore be noted that the most efficient agent in maintaining life

of the protected adrenalectomized dog, the amorphous fraction, is without effect upon carbohydrate metabolism even in the heaviest dosage.

It may be concluded as likely but not established beyond cavil that the various demands placed upon the adrenal cortex in the ordinary course of its life have been best served by the secretion of at least two hormones, one conserving salt and water and the other effecting efficient mobilization and utilization of carbohydrate. The provision of androgens and estrogens, somewhat special and poorly understood functions, not known to be of material importance to the maintenance of general well-being, requires separate, differentiated secretions, whether they be delivered from cells of recognizably different structure or not. The place of all of these in the physiologic expressions of adrenal neoplasms will be sought.

CLASSIFICATION OF THE SYNDROMES DUE TO ADRENAL CORTICAL TUMORS

All students of adrenal cortical tumors have been impressed by the variety of their manifestations. The clinical aspects are dealt with fully in Cahill's article of this series and will be briefly considered here only in so far as the association of particular symptoms and signs creates assumptions in regard to common pathogenesis. Taken in rough form and allowing freely for intergrades, I believe the following types would be acceptable to most workers:

1. Adrenogenital, occurring in children of either sex but more frequently in girls and occasionally in adult women. The masculinization is intense with precocious or heterosexual growth of the phallus, maturation of a masculine larynx, proliferation of body hair of masculine distribution, temporarily enhanced somatic growth in children and pronounced development of the musculature. Amenorrhea is usual in the female, and breast growth is usually held in abeyance. Similar expressions of adrenal hyperplasia in the young of either sex occur.

2. Cushing's syndrome, occuring in women and children. The masculinization is less intense than in the adrenogenital syndrome and is represented chiefly by hirsutism. Systemic disturbances including adiposity of the "buffalo type," plethoric appearance with the "moon face," hypertension, purple cutaneous striae, ecchymoses, osteoporosis and diabetes are frequent. Amenorrhea is the rule. Similar expressions are given by adrenal hyperplasia, thymic tumors with adrenal hyperplasia, and pituitary tumors with or without adrenal hyperplasia. A somewhat modified form, with loss rather than increase in body hair and with testicular atrophy, occurs rather rarely in men with pituitary tumors but has occurred only twice as an expression of adrenal tumors. Crooke's hyalinization of the basophiles of the pituitary body is characteristic of this type of disorder, irrespective of the tumor found.

3. Intergrades between Types 1 and 2, expressed for example by the

occurrence of obesity, hypertension, cutaneous striae and glycosuria, individually or together, in those in whom masculinization is intense.

4. Isolated expressions of the neoplasm, illustrated by the case of Sprague and his associates in which diabetes mellitus was the sole sign of the disease. Kepler and Keating[32] cite an instance in which amenorrhea was the sole endocrine stigma.

5. Feminization, a rare manifestation in men, characterized by atrophy of the testes, loss of body hair, and growth of the breasts. Unknown in the young boy it is expressed in larval form, complicated by other signs and symptoms, in a few cases in girls in which menstruation and breast development are precocious.

6. Tumors without endocrine manifestations.

The importance of distinguishing between the adrenogenital and Cushing's type was stressed by Haymaker and Anderson[33] in their excellent review of the subject and was given a metabolic emphasis by Albright and his associates,[25] who suggested that the disturbances in protein metabolism were largely anabolic in the first type and catabolic in the second. Cahill and associates,[34] accepting this same essential distinction from the strictly clinical standpoint, emphasized that contralateral adrenal atrophy was rare in the more virilistic form and common in the Cushing's form. Thompson and Eisenhardt[35] have pointed out that prior to 1940, the termination of their series, all eighteen patients with the typical Cushing syndrome, in which adrenal tumors were removed, died. Successful resection had been possible only in subjects with other expressions of adrenal hyperfunction. These authors also note that the Crooke changes were quite consistently found in the pituitaries of individuals with the fully evolved Cushing type of disorder but were absent in those integrades in which diabetes, hypertension, and virilization coexisted. The thorough review of Kepler and Keating[32] gives especial attention to the atypical cases reported. It seems to me that while a good deal is to be gained by classifying the signs and symptoms somewhat in this manner, that rigidity is to be avoided. Neither the clinical facts nor our knowledge of pathogenesis warrant sharp and inveterate distinctions between categories.

In the following account the more important symptoms and signs of adrenal tumors are considered individually and an attempt made to account for them in terms of the properties of adrenal secretions and their relatives.

HYPERTENSION

Sustained hypertension, often severe, is commonly found in the victims of adrenal cortical tumors. Among the most spectacular of numerous reports is the 11-month-old girl, reported by Marks, Thomas, and Warkany,[36] whose blood pressure was 245/145 mm. Hg. Renal defects sufficient to account for the hypertension have not been consistently found. In some subjects arteriolosclerotic lesions, even approaching

those of malignant nephrosclerosis, have been found in the kidneys at autopsy. In others no conspicuous defects were present. Very little data based upon the more elaborate and precise modern methods of measuring renal function are available.

Recent experience with desoxycorticosterone acetate in Addison's disease has provided us with our first clue as to the nature of the adrenal steroids responsible for this remarkable hypertension. Numerous physicians[11, 12, 37-39] using especially the heavy dosage of desoxycorticosterone acetate prevailing on the introduction of the substance observed that elevations of the blood pressure to 150 to 170 systolic, 90 to 110 diastolic were by no means uncommon. Thorn, Dorrance, and Day[12] found that 34 per cent of their sixty-four patients had a systolic blood pressure above 150, a diastolic above 100, or both at some time in the course of treatment. A value as high as 212/116 was observed by McCullagh and Ryan[38] in a man receiving 10 mg. of desoxycorticosterone acetate daily together with 10 Gm. of added salt. This hypertension occurs irregularly and may be transient. It may appear only after several weeks to months of treatment and may or may not be accompanied by gross edema. Thorn and Firor[39] thought that reduction of salt intake without altering the dose of the steroid would reduce the blood pressure and Loeb[40] recorded a similar experience in which salt alone produced hypertension, but these points have hardly been sufficiently well documented in an adequate number of patients as yet. Pre-existing hypertension may well be responsible in certain instances, but the experiments of Swingle and his associates[41] demonstrate that this is not necessary. Production of hypertension in normal individuals by this steroid has not been attempted.

Reported first by Kuhlmann and his associates,[42] induction of hypertension in dogs by desoxycorticosterone acetate has been studied in further detail by Swingle, Parkins, and Remington.[41] Adrenalectomized dogs in their experience, receiving 2 mg. of the steroid per day (eight to sixteen times the maintenance dose), showed an elevation of systolic blood pressure that began in forty-eight hours and continued for six to thirteen days at which time it stabilized in the neighborhood of 130 to 140 mm. of Hg, 20 to 30 mm. above normal levels. On cessation of excessive treatment the blood pressure slowly declined to normal within seven to ten days. One normal dog receiving the same treatment showed only a slight transient response. The plasma volume of the adrenalectomized dogs increased 30 to 40 per cent within three to seven days and then receded to slightly above the base line despite continued treatment. This together with the occasional complete dissociation between increased plasma volume and increased blood pressure led Swingle and his associates to discount any cause and effect relationship between the two.

Grollman, Harrison, and Williams[43] noted the production of an elevation of 40 mm. of Hg in rats receiving 0.5 mg. of desoxycorticosterone

acetate daily. This effect was prevented by the oral administration of a renal extract effective in reducing the blood pressure of rats with hypertension due to partial nephrectomy. The hypertensive influence of the steroid was held accordingly to involve a renal mechanism. Similar elevations in blood pressure in the rat were obtained with estradiol benzoate, stilbestrol, progesterone, and testosterone. The dosages used were enormous. No influence on the blood pressure of man with maximum therapeutic doses of these substances has been observed.

It can readily be seen from the foregoing that a beginning has been made in the study of the hypertensive effects of the steroids. Desoxycorticosterone is by no means the only one worthy of consideration. Although large amounts of adrenal extracts have not proved hypertensive, Swingle and his associates point out that such extracts share with desoxycorticosterone the power of protecting the adrenalectomized animal against the circulatory collapse and edema induced by transfusions of serum. The same group[14] later established that 17-hydroxy-11-dehydrocorticosterone was much more effective than desoxycorticosterone in protecting the adrenalectomized dog against collapse following manipulation of the intestines. It does not follow, of course, that such an agent in large amounts would be hypertensive but the matter is worth suitable inquiry.

SALT AND WATER METABOLISM

The swelling of the soft tissues of the face and eyes of certain patients with adrenal tumors may be in part due to salt and water retention in those tissues, and edema elsewhere may be due to hormonal influences on salt and water metabolism as well as to cardiac insufficiency. Polyuria and polydipsia not accounted for by glycosuria have been experienced by patients with the Cushing type of disorder. Complete and acceptable salt and water balance studies are not available. More attention has been paid to the concentration of serum electrolytes, chiefly in the victims of Cushing's syndrome not due to adrenal tumor, but it is well established that such changes in concentration often reflect disturbances in balance only sluggishly and hence do not substitute for exacting metabolic study.

In 1933 and 1934, Kepler and his associates [44, 45] called attention to the fact that occasional individuals with Cushing's syndrome showed a reduction in the concentration of chloride and potassium in the serum and an increase in bicarbonate. The 44-year-old woman reported by McQuarrie, Johnson, and Ziegler,[46] with Cushing's syndrome, showing slightly enlarged adrenals and Crooke's changes in the pituitary, illustrates these phenomena. Her serum bicarbonate was 38 meq. per liter; Cl, 89 meq. per liter; Na, 156 meq. per liter; K, 3.0 meq. per liter. The pH ranged from 7.55 to 7.60. An undetermined acidic fraction was present. Potassium chloride administration increased the

serum potassium and chloride and reduced the bicarbonate somewhat. Willson, Power, and Kepler[47] studied a man 39 years of age, with Cushing's syndrome, in whom operation disclosed no adrenal tumor. His serum Na of 137 meq. per liter was normal but his serum K was reduced to 2.2 meq., Cl to 78, and the bicarbonate was increased to 46 meq. per liter. Administration of 8 Gm. of potassium chloride per day (56 Gm. all told) yielded 26 Gm. to the body, of which only 2 Gm. could be assigned to extracellular fluids. This was interpreted as meaning previous exhaustion of potassium stores. Anderson, Haymaker, and Joseph[48] reported evidence suggesting increased urinary loss of potassium and retention of sodium in patients with Cushing's syndrome of unknown origin and Haymaker and Anderson[33] reported symptomatic improvement in patients receiving potassium citrate. The patient of Willson and his associates did not improve, however, despite correction of the anomalies in concentration of electrolytes. Kepler has on several occasions stressed the infrequency of alterations of serum electrolytes in Cushing's syndrome. In adrenal cortical tumors the only evidence of such changes that I know of is the level of 160 meq. of Na without alteration of K noted by Howard and Whitehead[49] in a patient with essentially virilistic manifestations and the data recorded in Table I,

TABLE I

CONCENTRATION OF SEVERAL SERUM CONSTITUENTS IN A 40-YEAR-OLD WOMAN SUFFERING FROM A PROVED MALIGNANT ADRENAL CORTICAL TUMOR*

DATE	CO_2 (MM. PER LITER)	Na (MM. PER LITER)	Cl (MM. PER LITER)	K (MM. PER LITER)	PH
1/22	39.1	147.2	93.1	5.5	7.52
1/30	40.2	152.6	90.4	3.14	7.53

*Courtesy of Dr. A. S. Alving.

secured by Dr. A. S. Alving, in a woman with Cushing's syndrome due to a malignant tumor of the adrenal cortex. These latter changes are essentially the same as those previously recorded in patients in which this syndrome occurred in the absence of adrenal tumors.

Progress toward explanation of the distorted electrolyte patterns seen in hyperadrenal states is now being made on the basis of our knowledge of the properties of large amounts of adrenal steroids. All writers on the subject have appreciated a possible analogy with the effects of desoxycorticosterone acetate. This substance induces retention of sodium, chloride, and water and impels renal excretion of potassium in the adrenalectomized dog and in Addison's disease in man. These effects are likewise seen at least temporarily in the normal of both species. The consequences of more protracted treatment with large amounts of desoxycorticosterone have been studied with care by Loeb, Ferrebee, and their associates in the normal dog[50, 51] and are complex. Prodigious thirst and ensuing polyuria supervene, apparently excited

by the rising sodium concentration in the serum, so that gross edema never occurs. Losses of potassium, however, continue. Serum potassium is depressed and a muscular paralysis relieved by potassium salts eventuates. As much as a third of the potassium content of skeletal muscle may be replaced by sodium.[51] Such a substitution of sodium for potassium likewise occurs in the rat,[52] but neither the muscular paralysis, the intense polyuria and polydipsia, nor edema are observed either in the rat[52] or the cat.[53] Necroses of heart and skeletal muscles in several species and hypertrophy of the renal tubules appear and may be duplilated by a low potassium diet.[54] Lowered serum potassium, only rarely inducing paralysis, has been observed in patients with Addison's disease receiving this steroid, but the effects of heavy protracted dosage in normal man are virtually unknown. Moehlig[55] and Jaffe have, however, seen polyuria and polydipsia in a patient with normal adrenals receiving large amounts of desoxycorticosterone acetate.

At first sight it would seem reasonable to see the influences of excessive amounts of a desoxycorticosterone like steroid in the distortion of electrolyte pattern, in the muscle weakness, and perhaps in the occasional edema and in the polyuria and polydipsia of certain of the victims of hyperfunction of the adrenal cortex. Close inspection, however, brings difficulties. The depression of serum chloride and elevation of bicarbonate seen in patients have not been induced in animals with desoxycorticosterone acetate although Heppel[56] did find such deviations in rats on a low potassium diet. Such blood volume determinations as have been made in Cushing's syndrome have been low, rather than high.[44] Loeb's measurements of muscle electrolytes in three subjects with Cushing's syndrome did not show modifications of electrolyte concentration, although he did not give either balances or serum electrolyte values on his subjects. None of these phenomena fit well with an uncomplicated desoxycorticosterone effect as far as this is now understood.

The secretion of large amounts of a steroid with a hydroxyl on carbon 17 would be expected to produce a different type of electrolyte disturbance than that given either by desoxycorticosterone or corticosterone. From the studies of Thorn and his associates[15, 16] in both dogs and man, an undue urinary loss of sodium, chloride, and water would be expected. Although not apparent in many of Thorn's experiments, potassium loss might occur eventually if tissue dissolution in the course of gluconeogenesis progresses for any length of time. If the androgens secreted by an adrenal tumor possess any of the metabolic properties of testosterone, and evidence will be adduced later that such seems very much the case in certain instances, the sodium, chloride, potassium, and water-retaining effects of the androgen[57, 58] would be superimposed upon any other effects present. The potassium retention induced by testosterone may even be accompanied by excessively low concentrations

of potassium in the serum of man without the appearance of paralytic phenomena, according to the recent work of Talbot, Butler, and MacLachlan.[59] The disposition of these various steroids to enhance one another in some respects, and to cancel one another in other respects, together with the likelihood that tumors may discharge all of these materials and more in varying quantities at various times, makes it entirely reasonable to expect a variety of disturbances in electrolyte balance in those with adrenal neoplasms. As suitable combinations of the various steroids are tested in animals and in man, more insight into the disturbances evoked by disease will be achieved.

OBESITY

Marks, Thomas, and Warkany[36] have recently reviewed the occurrence of obesity in children with adrenal cortical tumors and pointed out that extensive fat deposits may be generalized as well as localized to the trunk, neck, and face. The children may not weigh as much as their appearance suggests. Albright and his associates[25] and Newburgh[60] have called attention to the fact that protrusion of the abdomen due to laxity of abdominal muscles and bowing of the thoracic spine consequent upon loss of vertebral bony substance may provide more suggestion of obesity than careful scrutiny warrants. These comments were applied particularly to Cushing's syndrome in the adult without adrenal tumor, but may be extended to subjects in which adrenal tumors are found. Some of the fullness of the face may also be in part due to edema as well as to increased fat deposits. In the patient reported by Freyberg and Newburgh[61] fat was lost during an undernutrition program as well as in obesity of other origin. In this instance at least and probably in many if not all subjects, the fat deposits are mobilizable when nutritional need is urgent.

No adrenal steroid has as yet been shown to induce obesity. As mentioned previously, the precise role that intermediary fat metabolism plays in the organism's adjustment to the steroids reducing carbohydrate utilization and promoting gluconeogenesis is unknown but, judging from appearances, fat utilization increases rather than declines. Similarly, the efficiency of certain pituitary fractions in favoring transport of fat from other somatic depots to the liver is impaired by adrenalectomy.[62] No adrenal influence favoring accumulation of fat in somatic depots has thus far been suggested by experiment. While some obscure stimulation of appetite may well operate in the obese victims of adrenal tumors, and a sufficient intake of calories must be still considered a cardinal condition for the deposition of much adipose tissue, the localization of fat in certain areas in these subjects, as in other disorders, necessitates the assumption that specific factors affecting fat-bearing connective tissue exist and that humoral factors are among them. A more exact definition of the influence of the adrenal cortex on fat tissue is a matter for the future.

CARBOHYDRATE AND PROTEIN METABOLISM

It has long been known that diabetes mellitus occurs frequently among the symptoms of adrenal cortical tumors and that it occurs in those with Cushing's syndrome in whom no such tumor can be found. Lukens, Flippen, and Thigpen[63] record impaired glucose tolerance in one-half of fifty-five reported cases of adrenal carcinoma, adenoma, or bilateral hyperplasia. Glycosuria was considerable in nineteen. Such glycosuria may be abolished by dietary restrictions,[64] or may require relatively large doses of insulin, up to 145 units a day.[65] Even when the diabetes is mild, insulin may have less effect than would be expected when given in conjunction with glucose,[66] but in other instances there seems to be nothing unusual about the amounts of insulin required to control glycosuria.[67] Diabetes is usually associated with hirsutism, hypertension, amenorrhea, and obesity and frequently with a dusky skin and colored cutaneous striae[64] but may, as in the remarkable case of Sprague and his associates, represent the sole endocrine expression of the tumor.[65] It is apparently rare in those instances of adrenal hyperplasia or neoplasia in girls or young women in which vigorous masculinization is the predominating feature of the illness. Visible lesions of the pancreas do not seem to account for the diabetes,[63] but it is difficult to eliminate the predisposing force of latent diabetes mellitus in the ordinary sense.[32, 64] An elevation of the basal metabolic rate is frequently but by no means always associated with the diabetes.[64] If increased thyroid secretion is responsible for such elevation, the familiar influences of hyperthyroidism in impairing glucose tolerance may well be contributory.

Woodyatt[68] observed that in a man with Cushing's syndrome of unestablished etiology, but improved by x-ray therapy to the pituitary body, the urinary urea excretion was exceptionally high even when the glycosuria was controlled by insulin. On a diet adequate in calories and containing 81 Gm. of protein, 20 to 24 Gm. of nitrogen (equivalent to 125 to 150 Gm. of protein) were found daily in the urine. Balance could eventually be achieved by increasing the protein intake. Woodyatt suggested that the polyuria, up to 6,700 c.c. daily, might be accounted for by the high rate of nitrogen excretion. These observations were fully confirmed when the patient went to Boston under the care of Cushing. At this time the protein in the diet had to be increased to as much as 475 Gm. per day to maintain balance.

The discovery of the disposition of adrenal extracts and especially of adrenal steroids with an oxygen at carbon 11 to favor the mobilization of glucose and to restrict its disposal led to a rational theory of the mechanism of diabetes mellitus induced by adrenal tumors. Lukens and his associates[63] and C. N. H. Long introduced this view. While at first glycosuria was induced by adrenal agents only in the depancreatized animal, Ingle[69] has recently succeeded in producing severe

glycosuria in intact rats fed a high carbohydrate diet with large amounts of 17-hydroxy-11-dehydrocorticosterone. Urinary nitrogen increased also, but not sufficiently to account for the glucose excreted. In other experiments as previously mentioned, such a loss of nitrogen during gluconeogenesis was accompanied by discharge of phosphorus and under some circumstances at least by potassium.[7] Such catabolic effects presumably operate in the inhibition of somatic growth of normal young rats induced by heavy dosages of 11-oxygenated steroids,[22] although glycosuria was not recorded as occurring in these particular animals. Under other circumstances, however, as in the depancreatized dog described by Kendall,[1] glycosuria was enhanced by compound E without increasing urinary nitrogen excretion. It may be fairly said that it is not as yet entirely clear as to when the gluconeogenic process will predominate in the response to these steroids and when other events, now usually interpreted as meaning restricted glucose consumption, are of most importance. It may well be that the heavier the dose of the steroid, the more decisive is the role of gluconeogenesis. The capacity of the pancreas to secrete insulin may be expected to determine the extent of the opposition to such processes, at least in part. A basis for an understanding of the diabetes and occasional severe nitrogen loss in terms of the excessive action of known adrenal steroids is thus seen to be established, although many details require elucidation.

With the frequency of diabetes in Cushing's syndrome in mind and supported by the observation of Woodyatt on urinary nitrogen losses, and by the demonstration of the catabolic effects of several adrenal steroids, Albright and his associates[25] have formulated a bold general theory of the pathogenesis of the signs of Cushing's syndrome. No attempt was made to account for the hypertension. The predominately anabolic phenomena in those subjects with intense masculinization were explicitly excluded.

By protein wastage in the course of gluconeogenesis, Albright seeks to account for:

1. The wasting of muscle with consequent weakness
2. The thinning of the integument with the appearance of striae and rubor
3. The simulation of obesity by the loss of effective muscular and cutaneous support.
4. The loss of bone matrix with consequent osteoporosis
5. The thinning of arteriolar and venous walls with resulting fragility and hemorrhage

Albright and his associates suggested that testosterone by virtue of its anabolic effects might serve to counteract and repair the damage wrought by such tissue protein dissolution. They succeeded in inducing nitrogen and phosphorous retention in these subjects with testosterone

propionate in much the same manner as had previously been observed in eunuchoids[58, 70] and in normal men and women.[57, 70] They furthermore demonstrated a remarkable delayed retention of calcium that had not heretofore been observed with the androgen. The improvement of their patients increased their confidence in the soundness of their views.

The stark simplicity of this comprehensive theory may not survive. Albright[71] has already attempted to adapt it to new facts. It has not been possible as yet to demonstrate that the extraordinary nitrogen deficits observed by Woodyatt are of general and frequent occurrence. In none of the nitrogen balances recorded by Albright and his associates[25, 71] in Cushing's syndrome has any such nitrogen loss been found, nor was it apparent in the briefer studies of Willson[47] or Paschkis[67] and their respective co-workers. Indeed, Albright found that one such patient could conserve nitrogen as well or better than normal subjects when placed on a low protein diet.[71] The possibility remains that nitrogen deficits had occurred in the past in these subjects and that the protein stores were so depleted that there was little more readily mobilizable nitrogen to dissipate. Only further metabolic studies at all stages of the disease can settle this point. I am inclined to feel that such nitrogen losses as Woodyatt obtained must be due to relatively intense stimulation of gluconeogenesis by large amounts of steroids with an oxygen at carbon 11, and that losses of protein from the body as a whole of sufficient magnitude to be detected in metabolic experiments are rare and may not be of general significance. Albright has attempted to surmount the difficulty by altering his concept of the action of the adrenal steroids from catabolic to antianabolic.[71] I am not yet clear as to the advantages accruing from this change in emphasis. Certainly specific tissues such as bone suffer destruction in Cushing's syndrome. The heart of the matter seems to lie in whether such phenomena can be conceived simply as an exaggeration of the normal effects of the carbon 11 oxygen-bearing steroids on the protein metabolism of these tissues. In suggesting this interpretation, Albright and his associates have provided our thinking with an important challenge although the complexities and uncertainties of the data now available render the ultimate fate of this hypothesis obscure.

It is known that some tumors of the adrenal cortex in the child induce unusual somatic growth for a time with rapid development of the musculature. These especially in the boy may lead to the "infant hercules" type or the "burly brewer's drayman." Considerable hypertrophy of the phallus, deepening of the voice, and growth of hair of masculine distribution usually accompany the excessive somatic growth. Neither corticosterone, its relatives with an oxygen at carbon 11, nor desoxycorticosterone possess androgenic properties sufficient to accomplish such transformations of the body, nor do they induce the re-

tention of nitrogen and phosphorus necessary for growth. Testosterone propionate and methyl testosterone, however, have been shown to produce metabolic responses compatible with tissue growth in the child, and in the normal and sexually underdeveloped man and woman.[58, 70, 72-75] Retention of nitrogen, inorganic phosphorus, sulfate, and potassium have been induced. Sodium and chloride retention do occur at least in the first phase of treatment, as with desoxycorticosterone and corticosterone, but expansion of the extracellular fluid compartments of the body do not, as a rule, seem excessive in long-term experiments. Calcium retention has been observed only in special circumstances,[25] but it seems likely to me that it too is a general reaction which will be clearly established when suitable experiments are carried out. Most of these influences may be exerted by as little as 5 mg. of testosterone propionate daily,[74, 75] amounts that are scarcely androgenic, so that the body is relatively sensitive to the anabolic effects of these steroids. Recently, numerous workers have demonstrated that actual growth in height and weight of undergrown, underdeveloped children may be produced by testosterone propionate,[76-78] methyltestosterone,[73, 79] and in boys by the testicular secretion as evoked by chorionic gonadotropin.[78, 80] It is thus possible now to account for the unusual somatic growth and superlative muscular development of boys with testicular tumors by the excessive delivery of androgenic hormones from the neoplastic testes. The somewhat similar clinical status of certain victims of adrenal hyperplasia and neoplasia suggests that the adrenal cortex secretes substances with similar androgenic and anabolic propensities at least under these circumstances. What this substance may be is unknown. The several androgens isolated from the adrenal cortex are not powerful and have not been tested for metabolic effect. Testosterone is not as yet known as an andrenal constituent. Although progesterone has been isolated from the adrenal cortex and has somewhat feeble androgenic properties in some species, its androgenic and metabolic effects as thus far known in man seem rather too indistinct to suggest any important role for this substance in the metabolic or androgenic expressions of adrenal tumors.

Masculinization in one form or another is a common part of the symptomatology of the adult female with adrenal tumors even though it is usually less extreme than in the child. Any metabolic action of the androgen secreted might be expected to oppose the nitrogen, phosphorus, sodium, chloride, potassium, and water-expelling forces of some steroids present in excess and to reinforce any sodium, chloride, potassium, and water-retaining forces of other steroids. Thus a further factor is introduced into the clinical melange. Difficulties experienced in accounting for the metabolic expressions of adrenal tumors in terms of the effects of the more typical adrenal steroids may hence be expected.

It should be mentioned briefly that the anabolic effects described here for the androgens are not inextricably bound with androgenicity in the

strict sense. Estradiol benzoate in large doses has certain anabolic effects resembling those of the androgens[75] and depression of estrogen secretion has been implicated in postmenopausal osteoporosis in man.[81] Several workers[71, 82] have speculated on the possibility that the normal adrenal might secrete some steroid with anabolic properties, which follows a metabolic path like that of testosterone in the body and yields in the urine such derivatives as androsterone and etiocholan-ol-one. The existence of such a substance and its role in the economy of the organism either in health or disease remain uncertain.

The reports of Wilkins, Fleischmann, and Howard[83] and Butler, Ross, and Talbot[84] describe the development of suprarenal insufficiency in children suffering from adrenal hyperplasia that expressed itself by unusual body growth and exceptional maturation of masculine secondary sex characters. The proliferating cortical cells were histologically unlike those of the normal adrenal and had displaced normal cortical tissue.[83] We thus have evidence for a specialized adrenal cell capable of secreting androgens and incapable of secreting typical adrenal hormones, evidence which, by the way, was never satisfactory to me in previous discussions of the "androgenic zone" of the human fetal cortex. Further illustration is provided that androgens will not effectively repair suprarenal insufficiency. Clearly one must consider not only what a neoplasm can do by secreting certain hormones in excess but what the viable normal residue can do. Some such considerations may help to clarify the obscure cases of collapse in newborn infants with hyperplastic adrenal cortices reviewed by Kepler and Keating[32] and may even be required in the study of the pathogenesis of the symptoms of other adrenal tumors.

BONES AND CALCIUM METABOLISM

The affected bones in Cushing's syndrome are atrophic with little evidence of cyst formation or of the osteoclastic reaction so common in hyperparathyroidism. Osteoid tissue bespeaking an especial difficulty in calcification has not been described, to my knowledge. Serum levels of calcium are normal, as a rule, while those of inorganic phosphorus may be low. Hypertrophy of the parathyroid glands is not a common autopsy finding although it has been observed.[33] In the patient reported by Freyberg and his associates,[85, 86] a boy with pituitary adenoma and extreme osteoporosis but curiously enough with atrophic adrenals, neither the striking hypercalciuria nor hyperphosphaturia characteristic of hyperparathyroidism could be found. In Aub's study[87] of one of Cushing's early cases, however, the urinary calcium was some four times the average normal on a low calcium diet, while the fecal calcium approached normal. Hypercalciuria under similar circumstances was recorded by Paschkis and his associates.[67] The calcium balance was not negative to any extent in the subjects of Albright and associates.[25] It

must be confessed that complete balance studies during known active phases of bone dissolution are few and that little data are available in subjects in which adrenal tumors are responsible. Certainly little evidence that hyperparathyroidism is a frequent factor has been adduced.

In the last section, Albright's view that the essential bone lesion lies in loss of protein matrix was discussed. A somewhat similar explanation was offered by the Boston group for the osteoporosis that may occur after the menopause in women.[81] In this latter instance estradiol benzoate induced retention of calcium and phosphorus although the technically difficult demonstration of bone repair has as yet not been accomplished. In Cushing's syndrome, although an estrogen deficit must often be present, estradiol benzoate did not produce a strongly positive calcium balance[25] and the osteoporosis of the patient reported by Paschkis and associates,[67] progressed during treatment with stilbestrol. The extent to which the damaged bone can be repaired by testosterone remains to be seen, although the positive calcium balance described by Albright and his associates during treatment with the androgen is encouraging. This influence is not specific for Cushing's syndrome as it has been seen in aged men with osteoporosis[88] and may be at least in some degree a general reaction to the androgen. Freyberg and Grant[86] had difficulty in increasing calcium absorption by increasing dietary calcium or by giving vitamin D, although injected calcium was well retained. This type of observation has not been extended. Experimental work in the effects of various adrenal steroids on the bones of animals together with controlled metabolic observations are clearly necessary for the proper understanding of the osteoporotic process.

The growth of the long bones and the trunk in the early phase of the adrenogenital syndrome is in all probability ascribable to the anabolic activities of the androgens. As mentioned previously, growth in height and increase in bone maturation have now been repeatedly induced in undergrown, underdeveloped children with several androgens. Similarly, the early closure of the epiphysis in these young people may be ascribed to the effects of the androgens, although experimental evidence in man is not as completed in this respect as one might wish.

CHANGES IN THE SKIN AND BLOOD VESSELS

Although rubor, purplish cutaneous striae, and a disposition to hemorrhage from superficial skin vessels are among the cardinal expressions of adrenal tumors, we lack convincing explanations for their occurrence. The evidence from infrared photography as to the thinness of the integument is of interest.[25] The extent that loss of protein from the skin and vessel walls either in the course of gluconeogenesis or otherwise is responsible remains uncertain although Albright's provocative

theory that this is decisive is worthy of attention. Protein loss in the course of other wasting disease does not give rubor and hemorrhage from small blood vessels and purple striae, but such protein loss may be controlled still by intact adrenals and hence differ from that induced by an adrenal cortex secreting without restraining influence. Thus, any hypothesis advanced requires further presuppositions for its support and has value chiefly in directing attention to the processes it would explain. Even detailed pathologic study of the affected tissues is now lacking.

The seborrhea and acne frequently seen are perhaps best ascribed to androgens or to some obscure relatives thereof. Androgens alone among hormonal agents are known to increase the activities of sebaceous glands.

THE GENITAL DYSTROPHIES

Masculinization due to adrenal tumors may be represented by little more than hirsutism, as in Cushing's syndrome, or may be a veritable inversion of the female organism with hirsutism, hypertrophy of the larynx, growth of the phallus, and maturation of masculine musculature. These latter features are often more conspicuous in children. In boys, precocious evolution of secondary sex characters may occur but tumors enhancing masculine attributes of adult men are excessively rare. All of these reactions, at least in incipient form, have now been produced in man by single androgens such as testosterone or methyl testosterone, and in the immature male by testicular secretions under the influence of chorionic gonadotropin. Steroids with typical adrenal properties are not materially androgenic, and progesterone, which will repair suprarenal insufficiency in some species and is faintly androgenic in some respects, seems hardly capable of such effects in man as far as is now known. Several androgenic steroids as previously described have been isolated from the adrenal cortex, but they are less potent than testosterone in biologic tests and their activity in man has not been examined. Nevertheless, if androstenedione or 17-hydroxy-progesterone were discharged in large amounts by a tumor, something in the direction of masculinization would be expected. Another weak androgen, dehydroisoandrosterone, has been isolated in large amounts from the urine of patients with adrenal tumors and may conceivably contribute to masculinization. It has not itself been obtained from the adrenal and if it is derived from some other steroid, its mother substance is undetermined. At present it must be granted that the actual androgenic adrenal secretion is unknown.

Testosterone in large amounts is inimical to the normal functioning of the ovary.[89, 90] Thus in the detailed studies of Geist and his associates[89] amounts exceeding 500 mg. per month will induce amenorrhea in adult women. On the basis of a large body of experimental work largely in lower forms, this interference is interpretable as due to inhibition

of the release of gonadotropic, follicle-stimulating secretions from the pituitary body. Direct interference with the peripheral effects of the estrogens, as on the vaginal mucosa of women[91] is in all probability involved as well. By either mechanism or both, the circulation of any large amount of androgens with such properties may be expected to militate against the normal evolution and maintenance of certain feminine attributes. This may well be responsible for the deficiencies in normal sex characters of girls and women suffering from adrenal tumors. In some cases, however, amenorrhea may occur without especially conspicuous masculinization. Consideration of such problems must be waived until the responsible adrenal androgens or their close chemical relatives are identified and examined for their influences upon the gonads. A further confusion is exemplified by the fact that some young boys with precocious development of secondary sex characters have shown premature spermatogenesis.[32] This is difficult to explain. Large amounts of androgens in man depress spermatogenesis[92] although obviously physiologic amounts do not. In several species androgens like testosterone, in certain doses under certain conditions, will sustain or induce sperm production. No such influence is known in man although the matter can hardly be said to have been thoroughly explored. This difficulty is cited to illustrate once more the obstacles met by too facile theoretical disposal of the signs of adrenal tumors.

Much speculation has surrounded attempts to seek an androgenic function for the adrenal in the course of its normal existence and to implicate special cell types in the secretion of such androgens. If such speculations can in the end be brought to firm earth, masculinization by adrenal tumors will become less difficult to understand. Mere exaggeration of a normal function will more nearly suffice as an explanation Otherwise neoplastic rejuvenation of heterotopic gonadal remnants or the secretion of some perverted metabolite must be invoked. Space cannot be given here for an extended discussion of this problem. Under some circumstances, as in the young male mouse, the adrenal does seem to serve as a vicarious androgen producer in the absence of the testis during a limited part of the life cycle.[93, 98] In the rat certain pituitary gonadotropins will evoke androgen production by the adrenal.[94] In the mouse a specialized juxtamedullary cortical zone (X zone) is present in infancy and involutes under the influence of the testis or of pregnancy.[95, 96] Analogies between this zone and certain juxtamedullary cells of the adult human suprarenal cortex, and more especially of the human fetal cortex, have been sought largely on cytologic grounds. Production of androgens by this zone in the fetus has been hypothesized and the term "androgenic" applied to it.[97] No substantial evidence as to the function of the fetal adrenal cortex has, however, been provided. Goldzieher's more recent view that it serves to secrete a gluconeogenic agent enabling the fetus to endure relative anoxia is as

satisfactory as any involving androgenic functions. Special staining methods led Vines[99] to suggest that fuchsinophilic granules were present in the cells of masculinizing adrenal tumors, or in the cells of hypertrophic adrenals, and not in normal postnatal adrenals. Goormatigh[100] emphasized that masculinizing tumors in his experience contained fuchsinophilic and siderophilic granules not present in indifferent or feminizing tumors and like juxtamedullary cells. A more recent account of the tumors or hyperplasias[83] giving rise both to androgenic phenomena and to suprarenal insufficiency cite histologic differences between the proliferating adrenal cells found and normal adrenal tissue, and provide material evidence that the androgen-secreting cells are incapable of forming the normal adrenal hormones. The relationships between such cells and those of the large zona reticularis of the fetal cortex do not, however, appear to be fully established.

The same general problem has been approached from a different angle. As will appear in a subsequent section, the urine of a castrate man or woman contains androsterone and etiocholan-ol-one, both of which have been identified as breakdown products of injected testosterone. In the castrate these substances presumably arise from some adrenal precursor which takes a metabolic course like testosterone in the organism. Androstenedione which has been isolated from adrenal extracts, for example, could do so. This precursor could be androgenic in its physiologic effects or possess anabolic properties resembling those of the androgens. Several, including the author, have entertained this possibility.[59, 71, 82] Albright and his associates[138] as well as Kepler[139] have sought to implicate adrenal androgens in the maintenance of axillary and pubic hair, especially in women, and the former group have stressed the possible importance of androgen deficits in limiting the growth of short women with primary ovarian insufficiency described by Varney[140] and Albright[138] and their respective associates. It may be concluded that while the normal human adrenal cortex may secrete substances which are active as physiologic androgens, that it has not as yet been incontrovertibly proved to do so. The androgenic urinary derivatives are excreted as biologically inactive conjugates. Their presence does not establish that either they or their precursors behave as physiologic androgens in the organism. Physiologic evidence must be sought and although promising, such evidence is still incomplete.

The situation with regard to the rare feminizing tumors seen in adult men is much the same as in the androgenic tumors. The growth of the breasts and the atrophy of the testis are in accord with the known effects of the estrogens in the male, and large amounts of estrogenic substances have been found in the urine of one such patient.[136] Estrone has been extracted from the adrenal cortex. Adrenal tumors arising in mice ovariectomized shortly after birth evoke intense estrogenic effects in their hosts.[101] Although it is well known that estrogens can be

found in the urine of castrated men or women, their function in the organism is obscure. Such estrogens may come from the adrenal cortex, but to what purpose is unknown. The recent demonstration by Shorr and his associates[102] that estrogens unlike androgens increase the urinary excretion of citrate and hence serve to protect the urinary tract from deposition of insoluble calcium salts and the work of Albright and his associates[81] implicating estrogens in the maintenance of bone emphasize the advances to be expected when attention is paid to the widely ramifying influences of the sex hormones. The extent to which estrogens residual after castration serve such or other nongenital functions is unknown although it seems to me that inquiry along these lines might be useful. It may be expected that when estrogens are circulating in large amounts in those with adrenal tumors that their metabolic as well as their genital effects may enter into the expressions of the disorder. Knowlton and her associates[75] have recently summarized these metabolic effects as far as man is concerned and presented additional data. In addition to favoring increased citrate excretion, as already mentioned, retention of sodium, chloride, nitrogen phosphorus, and, at least under some circumstances, calcium has been induced, by estradiol benzoate. Thus far, however, it does not seem likely that excessive secretion of estrogens frequently plays any major role in the expressions of adrenal tumors in man.

THE URINARY EXCRETORY PRODUCTS

Pincus and Hirschmann[103] have recently provided a complete review of the urinary derivatives of the biologically active steroid compounds, and Koch[104] and Doisy[105] have discussed the intermediary metabolism of the androgens and estrogens, respectively. When studies of urinary hormonal or better hormonelike substances were initiated, it was hoped that the pathologic physiology of much human disease would be promptly clarified. The upshot has been otherwise. A new and complex body of data appeared, related it is true to the expressions of disease, but related through the still obscure processes of the intermediary metabolism of the steroids. It is accordingly not possible now to read the hormone circulating in the body directly from a urinary assay, however painstaking such assay may be from the technical standpoint. Urinary studies form such a large part of the means by which the pathologic physiology of adrenal tumors will be eventually unraveled, however, that consideration will be given here to the available data. Unfortunately, the thoroughgoing and elaborate undertaking of Dobriner, Gordon, Lieberman, Fieser, and Rhoads which promises so much for the crystallization of our knowledge of this subject has been published only in preliminary form.[106]

The chief normal urinary steroids of 19-carbon atom series are:

1. androsterone (XIV)
2. etiocholan 3α ol 17 one (XVI)

3. dehydroisoandrosterone (XV)
4. isoandrosterone

Of these, androsterone and its stereoisomer etiocholan-ol-one are present in approximately equal amounts. Dobriner has kindly permitted me to quote the unpublished figures of his group as obtained by isolation procedures. Three normal young men excreted from 5.2 to 6.6 mg. of androsterone per day and from 4.9 to 8.1 mg. of etiocholan-ol-one per day. Two normal young women excreted from 3.0 to 3.1 mg. of androsterone and from 2.9 to 3.1 mg. of etiocholan-ol-one per day. Of these, androsterone alone is androgenic and accounts thus for the bulk of the androgenic activity of normal urine, which by the capon comb technique amounts to about 70 International Units per day (7 mg. equivalents of androsterone) in normal young men and somewhat less, in all probability, in normal young women. Dehydroisoandrosterone and isoandrosterone possess the β configuration at carbon 3 and are hence digitonin precipitable. Talbot and his associates[107] and Bauman and Metzger[108] give this β fraction as 10 per cent or less of the total 17-ketosteroids on the average. Dobriner's estimates are lower, while Munson, Gallagher, and Koch[109] account for about 20 per cent of the total 17-ketosteroids as dehydroisoandrosterone sulfate. Since dehydroisoandrosterone is from one-half to one-third as potent as androsterone and isoandrosterone about one-fifth as potent by the capon comb technique, these substances do not contribute greatly to the androgenicity of normal urine.

All of these steroids are present as conjugates which are biologically inactive, dehydroisoandrosterone as the sulfate,[109] and others possibly as glucuronides. They are freed by hydrolysis. Taken together they are commonly known as 17-ketosteroids, and measured as such, doubtless with other substances, by the red color given with metadinitrobenzene (Zimmerman reaction). They fall into the ketonic and alcoholic fractions, which make up the greater part of the mixture in normal urine yielding this color.

As determined first by the Callows,[110, 111] the components of the steroid mixture in the urine of normal men and women are the same, such difference as exists being quantitative, rather than qualitative. When testosterone is administered, the urinary excretion of at least androsterone and etiocholan-ol-one is increased[112, 113] so that these substances may be derived in part at least from the testis. Similarly, in the urine of a patient with a malignant interstitial cell tumor of the testis studied by Venning, Hoffman, and Browne[114] large amounts of androsterone sulfate were found. Neither in this patient nor in those receiving injections of testosterone was dehydroisoandrosterone part of the increment in urinary steroids. Castrated men[115] and women[116] excrete much the same type of 17-ketosteroids as normal men and

women. Castrated or sexually underdeveloped men have less androgenic activity in the urine than normal young men[117-119] but the overlap is substantial. The situation in castrated women is less clear. Total 17-ketosteroid excretion seems unaffected[120, 121] but androgens have been insufficiently studied. Quantitative variations in the amounts of the several steroids before and after castration in either sex, require much further study as exemplified by the anomalous rise in 17-ketosteroid excretion occurring late after the castration of older men in the experience of Scott and Vermenlen.[141] In Addison's disease 17-ketosteroid and androgen excretion is low probably especially in women.[120] The matter may be summarized by the statement that while part of the urinary androsterone and etiocholan-ol-one arises from the testis in the male that a nongonadal source must be sought for the remainder, and that a nongonadal source likewise must be sought for much if not all of similar compounds in the female. No gonadal source for dehydroisoandrosterone has been established. The adrenal by virtue of the steroid character of its hormones comes naturally to mind as a source for these substances.

The urine of patients with adrenal cancer has long been known to contain often excessive amounts of androgenic material.[117] Callow[122, 123] first examined the nature of the androgens present. In a 6-year-old girl exhibiting a Cushing type of disorder as much as 70 mg. of dehydroisoandrosterone was obtained from a liter of urine, as compared to 0.1 to 0.2 mg. per liter obtained from normal dults. The dehydroisoandrosterone accounted for 70 per cent of the androgenic activity. Callow observed this in other patients and it has been confirmed further by Wolfe, Fieser, and Friedgood[124] and Dorfman and associates[125] by isolation procedures and approximately by Talbot[107, 127] and Dobriner[106] and their respective associates measuring the 3-β or digitonin precipitable fractions of urine. It is not known whether dehydroisoandrosterone is secreted as such or whether it is derived from some precursor. No injected steroid save dehydroisoandrosterone itself[109] has been shown to yield this steroid in the urine although examination of the matter must be said to be fragmentary thus far. Nor is it clear that excessive excretion of 3-β steroids can be correlated with any particular clinical expression of the disease. In Cushing's syndrome not due to adrenal tumors, 17-ketosteroid excretion may be normal[120] and the β fraction not unusual.[107] In adrenal tumors producing the more strictly adrenogenital form of disorder, dehydroisoandrosterone excretion[125] or β fraction excretion has been high. It has by no means been shown that all increased androgenic activity in the urine of subjects with adrenal tumors or hyperplasia is consistently due to dehydroisoandrosterone. Androsterone may contribute to the enhanced activity. The physiologic potentialities of dehydroisoandrosterone itself in man are insufficiently explored so that it is not possible to envisage clearly the effects of this material in patients with adrenal tumors.

Others of the 17-ketosteroids may be present in excess in patients with adrenal tumors. Etiocholan-ol-one was greatly increased in the urine of a subject reported by Wolfe, Fieser, and Friedgood[124] at a time when little androsterone was present. The significance of this is uncertain. δ-3-5 androstadienone-17 has been found on several occasions both in feminizing[125] and masculinizing tumors[122] and the presence of this and other poorly understood substances either excreted directly or arising in the course of manipulation of the urine requires explanation. Talbot, Butler, and Berman[127] report unusual amounts of nonalcoholic 17-ketosteroids in patients with cancer of the adrenal as compared with those with adrenal hyperplasia.

It may be held as likely that none of the adrenal hormones serving to maintain life contribute materially to the urinary 17-ketosteroids. This presumption is possible even in the absence of suitable experiments in which adrenal steroids have been injected into man and their derivatives followed in the urine. Children excrete very little 17-ketosteroid or androgenic material in their urine. The increase in these substances in both sexes at puberty bespeaks some function evolving at that time and not some function essential to life. As mentioned previously, the adrenal function involved may have something to do with secondary sex characters or with anabolic effects like those of testosterone. This matter may be considered uncertain at present. It must be noted that urinary androgens are excreted as biologically active conjugates and those events that are of utmost physiologic importance occur prior to this conjugation.

Anderson and her associates[48] first presented evidence that a life-sustaining, adrenocortical-like compound was present in excessive amounts in the blood and urine of patients with Cushing's syndrome. Weil and Browne[128] using Selye and Schenker's[129] test of improvement in the endurance to cold of adrenalectomized rats found cortical material in the urine of several patients including those subjected to operations. This test has been further utilized by Dorfman and his colleagues[130] and by the Montreal group,[131] and a substance or substances found in normal urine which will sustain life of adrenalectomized rats, improve tolerance to cold, increase resistance to fatigue in electrically stimulated muscle, and increase liver glycogen. These are the properties of adrenal extracts and taken together suggest the presence of a corticosterone-like compound. The further application of such biologic tests to the urine of patients with adrenal tumors will be of importance.

Biologically inactive alcohols of the 21-carbon atom series have been isolated from the urine of patients with adrenal tumors or adrenal hyperplasia. Butler and Marrian[132] isolated pregnane-3, 17, 20-triol from the urine of women with virilism. Venning, Weil, and Browne[133] later found substantial amounts of pregnanediol glucuronide in the

urine of a woman with an adrenal tumor in which there was no vestige of ovarian function. This has now been repeatedly confirmed both in girls and women with adrenal hyperplasia,[67, 127] although it is not a constant finding.[127] Since progesterone is the source of this substance in the latter half of the normal menstrual cycle and since progesterone has been found in the adrenal cortex, this substance could be the precursor in patients with adrenal hyperfunction. Desoxycorticosterone likewise yields urinary pregnanediol glucuronide however[134] and other steroids may do so. Thus far the appearance of pregnanediol does not seem to be strictly correlated with any special type of clinical disorder, appearing both in intensely masculinized girls showing little or none of the Cushing phenomena[127] and in woman with the typical Cushing syndrome.[67]

Frank[135] demonstrated the presence of large amounts of estrogens in the urine of a masculinized woman with an adrenal cortical carcinoma. This seems to be an infrequent finding.[117] Simpson and Joll[136] demonstrated large amounts of estrogenic activity in the urine of a man with a feminizing tumor establishing a correlation with the symptoms and signs of the disorder. Frank's experience is frankly paradoxical. One must conclude that in his case conjugation of the estrogens occurred before an opportunity to influence the organism was provided. Estrone is present in the adrenal cortex but other steroids may yield estrogens somewhere in the course of their activity. Testosterone propionate, for example, has repeatedly been shown to do so.

The confusion surrounding the physiologic meaning of the urinary excretion of steroids will be gradually surmounted as more of the adrenal agents become available in sufficient amount and in sufficient purity for administration to man. The economy of lower species with respect to urinary steroids is so different from that of the human being that little directly applicable information is to be gained from them.

MISCELLANEOUS

It is a common and dangerous experience to find the contralateral adrenal gland atrophic in the presence of an adrenal cortical tumor. Cahill and his associates[34] and Thompson and Eisenhardt[35] have pointed out that this atrophy is likely to be profound when the clinical expressions of the disease are those of Cushing's syndrome and is less conspicuous in the adrenogenital syndrome. Experimental findings are in accord with this distinction. Cortical extracts induce atrophy of the normal adrenals, an influence which may be exerted through inhibition of pituitary adrenotropic secretion, since pituitary adrenotropins will prevent this adrenal inhibition. Corticosterone and 11-dehydro-17-hydroxycorticosterone seem most effective in this regard, desoxycorticosterone less so, although the latter compound in Selye's

experience will induce atrophy in large dosage. The androgens do not materially inhibit the adrenal cortex, save in the case of specialized X zone of the mouse. It is therefore reasonable that victims of tumors in which masculinization predominates should have better preserved cortical tissue than those in which excess of the more typical adrenal secretions exists.

Several cortical steroids and cortical extracts as well as the gonadal hormones induce atrophy of the thymus gland in experimental animals. Thymic involution, however, is so common in man with all types of illness that it will be impossible to relate thymic involution to the expressions of adrenal tumors with any degree of accuracy. Occasional exceptions to this expected thymic involution are, however, of a good deal of theoretical interest. Thus, Freyberg's patient[85] with manifest Cushing's syndrome and atrophic adrenals had a very large thymus. The chief lesion in this instance was a pituitary adenoma. One cannot help but raise the question as to whether the manifestations of the disorder were not due to direct pituitary influence on tissues rather than to increased adrenal secretion secondary to pituitary stimulation. Thymic involution would have been expected had the syndrome been due to excess of compounds like corticosterone.

This same question has been raised by Crooke,[137] who described hyalinization of pituitary basophiles in Cushing's syndrome irrespective of whether adrenal tumors, adrenal hyperplasia, pituitary tumors, or thymic tumors were present or not. Students of the subject have generally come to agree with Crooke's findings, and Thompson and Eisenhardt have stressed the uniformity of these basophile changes in patients with adrenal tumors in which Cushing's syndrome was fully evolved. The disposition, however, to see in this common lesion an expression of pituitary hyperactivity and to attribute many of the expressions of the disease to pituitary hyperfunction has not found favor. The reasons for this are obvious enough. Cytologists have not been able to agree as to whether the Crooke changes represent increased secretory function or whether they are degenerative. Adrenotropic pituitary secretions are well known and the functions of the adrenal under such stimulation seem much like those of large amounts of cortical extract, or of adrenal steroids in excess. Very little is known of the reverse influence of the adrenal cortex on the pituitary body. Most effects of adrenal extracts on carbohydrate metabolism seem well exhibited in the hypophysectomized animal.[8] With the exception of the capacity to induce atrophy of the normal adrenal cortex, few if any of the properties of adrenal steroids are known to be exerted through the anterior lobe. When a chain of events occurs, therefore, in which both pituitary and adrenal cortex are involved, one is at the present time most likely to consider the pituitary as stimulating the adrenal cortex rather than the reverse. It must be admitted, however, that patients

like that of Freyberg and his associates[85] are somewhat disquieting. Further attention to the Crooke phenomena will doubtless be given in the future and attempts to induce the hyalin changes in pituitary basophiles with pure adrenal steroids in excess will be made. If such can be done and the effects correlated with physiologic response in normal and hypophysectomized animals the extent to which the particular steroid operates through the hypophysis can be determined. Until such work is accomplished it will be difficult to rest easy in our usual assumption that most of the expressions of adrenal tumors are due to the direct peripheral action of the adrenal steroids. The occasional presence of advanced spermatogenesis in boys with precocious puberty due to adrenal tumors speaks to the same point, since the question of participation of the hypophysis must be raised and for the present left unanswered.

SUMMARY

1. Some twenty-eight compounds have now been isolated from the suprarenal cortex. A number of these such as corticosterone and desoxycorticosterone effectively repair those disturbances of salt and water metabolism characteristic of suprarenal insufficiency. Those with an oxygen at carbon 11, such as corticosterone and 17-hydroxy-11-dehydrocorticosterone, repair defects in carbohydrate and protein metabolism characteristic of suprarenal insufficiency. Certain of the 17-hydroxyl compounds favor urinary sodium and chloride loss. An amorphous fraction has been isolated which is more powerful in sustaining the life of the adrenalectomized dog than any known pure steroid. Progesterone, several androgens, estrone, and several compounds, inert by biological assays thus far made, have also been obtained.

2. It is likely that at least two secretions are necessary to repair suprarenal defects and that androgenic or estrogenic functions require the formation of separate differentiated hormones.

3. The following signs and symptoms of adrenal tumors have been reproduced to some extent by pure steroids:

(a) Hypertension by desoxycorticosterone acetate.

(b) Sodium, chloride, and water retention and potassium loss by desoxycorticosterone and corticosterone. The electrolyte pattern in the serum of patients, however, is not completely accounted for by these steroids.

(c) Diabetes mellitus and nitrogen loss by compounds such as corticosterone and 17-hydroxy-11-dehydrocorticosterone, especially in the presence of reduced insulin secretion.

(d) Nitrogen retention and somatic growth by testosterone and its relatives.

(e) The masculinization and the feminization, respectively, together with depression of gonadal function, by androgens and estrogens.

(f) Atrophy of the contralateral adrenal cortex by corticosterone and 17-hydroxy-11-dehydrocorticosterone.

It is pointed out that metabolic balances in the victims of adrenal tumors are often meager and that such balances may be expected to vary from person to person depending on the active steroids secreted. The known steroids may serve to counterbalance one another if mixed in proper proportion by the tumor.

4. The following signs and symptoms of adrenal tumors are not yet accounted for although hypotheses exist which promise with suitable modification, to be useful in the future.

(a) The osteoporosis

(b) Cutaneous rubor, striae, and ecchymoses

(c) Adiposity

(d) Polyuria and polydipsia

(e) Muscular weakness

5. A number of interesting steroids have been found in excessive amounts in the urine of the victims of adrenal tumors. The precursors of these steroids and their function in the body are, however, obscure.

6. Further elaboration of almost every point is necessary before the actual secretions of adrenal tumors can be identified. The suggestions made in the foregoing are often the merest approximations and indicate the direction that contemporary research is taking toward the solution of the problems involved.

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HORMONAL TUMORS OF THE ADRENAL

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THERE is perhaps no more fascinating study among all tumors than that dealing with the bizarre symptoms of those occurring in the hormonal glands. When tumors appear in which hormones are produced, syndromes occur in the individual due to the effect of the abnormal amount of hormone or hormones elaborated. In certain rare instances perverted hormones may be produced by tumor cells. Among the tumors occurring in the hormonal glands, the adrenal presents as wide a variety as any other in its diversification of symptoms, and in this resembles the pituitary; often the symptoms from dyscrasia of these two glands resemble each other. When tumors occur in the adrenal, they may be either of the cortex or of the medulla, and in either they may produce hormones or they may not.

In 1928, at the Squier Clinic of the Presbyterian Hospital, we became interested in the study of an adrenal cortical tumor and in conjunction with other departments have studied a number of these cases. A review of this study is presented.

Because of a much clearer understanding of the clinical status of the adrenal to its physiologic functions and pathologic changes, the more recent studies of its embryology and biologic processes are interesting.

The mammalian adrenal is actually two glands fused together in development. Each of the glands has an essentially different origin, a different type of tissue, and a separate function. They happen to be enclosed in one enveloping capsule and tissue stroma. The adrenals are normally situated in the outer layer of the renal capsule above each kidney. Recently O'Crowley and Martland have shown that occasionally they may be closely attached to the kidney and rarely may be under the true capsule of the kidney itself. Accessory adrenals occur, are of cortical tissue, and have been called Marchand's bodies. They have been described as of the kidney, the perirenal fascia, the retroperitoneal fascia, within the broad ligament, attached to the ovary, or associated with gonadal testicular tissues. Tumors of these adrenals have occurred, all of the cortical type, and with and without similar syndromes as are seen with adrenal cortical tumors.

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THE ADRENAL CORTEX

The adrenal cortex originates from the mesoderm of the colon epithelium near the genital ridge. The cortex during postnatal life gradually forms into three microscopic layers, which are completed at or about puberty. The development of the inner of these three layers just before puberty has been shown by Miller, Deansley, and Whitehead to have some connection with the development at that time of the sexual glands and organs. Because of increase in size of the layer at this time it was suggested as an X zone of the adrenal. A further elaboration of this suggestion was made by Grollman, who suggested that the inside cells of the inner layer may be androgenic cells, and he described this as an androgenic layer to explain the effects from its suggested function.

A clearer explanation of the development and growth of the adrenal cortex has been furnished by the studies of Bogomoloz, Goormaghligh, Hoerr, and Zwemer, in which they have shown that the adrenal cortex apparently grows continuously during life from without inward. New cells are constantly formed from the spindle-shaped cells under the fibrous capsule, and in their growth develop from without inward the zona glomerulosa, the zona fasciculosa, and the zona reticulosa. During this process they elaborate, accumulate, and discharge lipoid sterol and then, degenerating, are absorbed in the reticulosa near the medulla. The elaborated material is discharged into the capillaries by the mature cells before their degeneration, and the process is constant, with replacement by new cells. The removal of the degenerated cells is by macrophages and microphages near the medulla.

There may be hypoactivity of the process as well as hyperactivity. Under certain phases of hyperactivity, normal or pathologic, there may appear to be larger numbers of cells undergoing degeneration than are normally seen. When this occurs, it may be the reason for the widening of the "reticulate zone at puberty" (Deansley and Miller) or the special zone "androgenic" (Grollman), and the larger number of cells with degenerative fuchsinophilic staining granules as reported by Broster and Vines.

THE PHYSIOLOGY OF THE ADRENAL CORTEX

The adrenal cortex has been definitely established as the elaborator of hormonal substances, some of which are necessary for life maintenance. These hormonal substances have been shown chemically to be sterol lipoids.

Many closely related sterol derivates have been prepared from the adrenal cortex. Some have had definite hormonal action. The action of some has effects upon the salt and water metabolism, the electrolyte balance, the permeability of the capillaries, the regulation of the carbohydrate fat and protein metabolism, the renal function, the capacity of muscle response, and the resistance to stress. The maintenance of life

and health is probably due to a combination of the various activities of the steroids. Of the identified steroids, one desoxycorticosterone seems to be most effective in the regulation of the salt and water metabolism, the electrolyte balance, in capillary permeability, and in the preservation of renal function, but it apparently does not include many of the other hormonal functions of the adrenal, particularly that of carbohydrate metabolism.

Another of the identified steroids occurring in the substance of the adrenal cortical cells is one with the property of male hormone (dehydro-iso-androsterone). This differs slightly from the testicular male hormone (androsterone), which has also been described as being produced by the adrenal cortex. There has been also identified as secreted by normal adrenals the female hormones, estrone and progesterone. Thus, normal adrenals have the power to elaborate both male and female sex hormones. Part of the hormones occurring in the urine of normal males and females is considered to be derived from the adrenal.

From the multitude of experiments reported, there are many suggestions that the adrenals are implicated in many other metabolic processes. There has been shown that there is a relationship between the adrenal cortex and the pituitary and gonads, and that hyperactivity of the ovary may partially replace adrenal function. It is now suggested clinically that adrenal function may partially replace testicular function. In addition, the adrenal has been suggested as one of the regulators of vitamin balance. It has been shown to have relatively large amounts of vitamin C in its cortical cells.

PATHOLOGIC PHYSIOLOGY

Since the adrenal cortex is composed of hormonal secreting cells, there are periods of cell growth or cell degeneration in which hormones are not elaborated. Tumor or hyperplasia of immature cells only will not increase the hormones delivered into the capillaries. Such tumors, when they occur, are nonhormonal. However, hyperplasia or tumor of cells that have matured will elaborate and secrete into the capillaries excess hormones over normal because of the increase of number of cells. The hormones may apparently be of all the steroids, or, as has been suggested by clinicopathologic studies, only excesses of certain hormones may be produced. Such has been shown to be the result of hyperplasia or tumor in the adrenogenital syndrome, in which the excess amount of male hormones elaborated by the tumor has its effect upon the secondary sex organs. This has been shown to occur in the masculinization of females, both children and adults, and in the male maturity of male children.

Other tumors have occurred in which the excess hormone elaborated has female hormonal activity. Thus, Burrows and co-workers and

Simpson and Joll have shown the feminism of a male to be the result of excess estrogens elaborated by a tumor of the adrenal cortex. In earlier reports Cahill, as well as Frank, have shown that high amounts of estrogens occur in the urine of females with adrenal cortical tumors, although the hormonal effect upon these individuals has been that usually produced by excess male hormones.

The syndrome described under many variations as Cushing's has been contended by Bauer to be due to an excess of the adrenal cortical hormones, which have to do with the regulation of the electrolytes, salt and water, and fat and sugar metabolism, and are produced by the adrenal cortex, either in hyperplasia secondary to pituitary effect or in tumor of the adrenal itself. There have been many supporters of this theory, both from experimental and clinical observation.

It has been well established that the adrenal thus can elaborate androgens and estrogens, as well as other metabolic hormonal steroids; that these hormones may be present in excess quantities in hyperplasia and tumor and can be responsible for the symptoms present. There may be produced an increase of normal hormones, and, as has been shown, abnormal hormones may be produced by tumor cells. Such is the conclusion of the report of Butler and Marrian, in which a steroid with male hormonal properties (pregnane 3, 17, 20 triol) was found in the urine in a case of adrenal cortical tumor; they established the fact that such a hormone is not excreted by normal man or from a normal or pregnant woman. The possible finding of other abnormal steroids awaits similar investigation of other cases.

CLINICAL CLASSIFICATION OF TUMORS

Since the beginning of our interest in cases of syndromes due to adrenal changes, some with few and others with many symptoms suggesting adrenal pathology, hundreds of cases were studied. From the large number examined and after a serious attempt to prove either the presence or absence of tumor, the conclusion has been drawn that adrenal syndromes may be often due to adrenal pathologic physiology, but they are rarely due to actual tumor. When tumors do occur with hormonal changes, these symptoms vary according to the hormones secreted, their amount, and the age and sex of the individual so afflicted.

On the basis of proved cases, the following clinical groups of adrenal cortical tumors have been previously described (Cahill, Melicow, and Darby):

1. No recognizable hormonal changes
2. Changes due to excess androgens
   a) In female child toward adult masculinity
   b) In female adult toward masculinity
   c) In male child toward adult masculinity

3. Changes due to excess estrogens
   a) In adult male toward feminity
4. Changes due to excess androgens and other steroids
   a) Cushing's syndrome with associated sexual changes (mostly in females)
5. Changes due to excess of other steroids related to metabolism
   a) Cushing's syndrome without sexual changes (in male and female)

TUMORS WITH SYMPTOMS DUE TO EXCESS ANDROGENS

In the Female Child.—Thomas Cook, in 1765, first described a child with changes undoubtedly due to excess androgens. This was followed by Bevan and Romkild in 1802, Telesius in 1803, Ogle in 1865, and Colcott, Fox, and Ogston. Because of the dramatic changes this type was recorded early. The occurrence in female children is not frequent but forms a fair percentage of the recorded adrenal tumors.

When the disease occurs before birth or in early infancy in the female child, the symptoms have been described as pseudohermaphroditism. Gallais thought that true hermaphroditism could occur if an adrenal cortical tumor was present early in fetal life, but that is no longer held tenable. When pseudohermaphroditism occurs after birth a hypersecretion of the adrenal cortex, whether due to hyperplasia or tumor, may definitely be the cause of the syndrome. In these children all degrees of secondary sex changes are found, from only a slight enlargement of the clitoris to an enormous size like a penis, accompanied by atresia or absence of the vagina. The internal genitals are usually small and sometimes deformed.

From the work of Green, Ivy, and others, it is strongly suggested that the syndrome of pseudohermaphroditism of birth and perhaps early infancy, when not due to definite adrenal hypertrophy or tumor, may be the result of the effect of abnormal hormonal activity of the mother upon the fetus during gestation.

The occurrence of female pseudohermaphroditism is not frequent. Five of these children have been studied for a number of years. Two were seen at 3, one at 4, one at 5, and one at 9 years of age. The condition of all began early in life with the hypertrophy of the clitoris, with the appearance of hair upon the genitals, excessive body growth for a while, increase in musculature, deepening of voice, accelerated epiphyseal and dental development, and a higher mental aptitude than their normal age level. In all, androgens were demonstrated in the urine. Air-insufflation roentgenograms showed the adrenals well in all. Four had apparently a bilateral increase in size. Complete operative explorations showed female internal organs. Biopsies of the ovaries showed no testicular cell inclusions. Section of the adrenals showed an apparent age acceleration in the adrenal zones and cells. None of

the children with these syndromes have shown any evidence of adrenal tumor, and some have been observed for several years. All have had amputation of the penile clitoris. Those who had the adrenals sectioned had the hormonal output apparently temporarily diminished. All have shown marked symptomatic improvement with administration of a potent female hormone.

From the literature these syndromal cases are not uncommon. The causation of these symptoms by tumor is infrequent, but that tumor can be the cause of pseudosexual precocity is amply supported in the report by Reilly, Lisser, and Hinman, in which they cite their case of a child of 22 months with pseudosexual precocity only, due to an adrenal cortical tumor. Microscopically it was a carcinoma of the adrenal cortex. In a compilation of the literature they found forty cases of pseudosexual precocity. Of thirteen patients with pseudosexual precocity alone, two were shown to have tumor, and these tumors were successfully removed. They found three reported cases of successful removal of aberrant adrenal tissue tumors producing the same syndrome. None of these successful cases showed the other symptoms associated with the Cushing syndrome. They found records of ten patients in whom tumors were present with the syndrome, all of whom died either during operation or within three days. Two of these had symptoms of the Cushing type. They recorded fifteen cases without operation, in which adrenal cortical tumors were found on autopsy. In eight of these symptoms suggestive of hormonal influence of the Cushing type were found: obesity, bloatedness, flabbiness, glycosuria, and osteoporosis.

The older children in prepuberty usually do not menstruate, even though the period of puberty has been reached. There have been four recorded cases of menstruation in these children. It is possible that some of these tumors may have secreted estrogens, but as yet no reports of this finding have been recorded.

The older children are more apt to develop a more general hirsutism, on the face and chest as well as the body. Deepening of the voice is often present. There is usually transitory, rapid growth, followed by closure of the epiphyses and a later relative shortness of the individual.

The operative results in these children have been good, considering the seriousness of the hormonal effects. Collett was the first, in 1924, to report a successful removal in a child. Up to 1939, Lisser was able to collect seven successful cases. From the description of the cases, the successful results were among those apparently with only sex syndromes. Among the records of the unsuccessful results have been recorded symptoms suggestive of other metabolic changes. Ten patients dying at operation or within three days suggest that, beside surgical shock, acute adrenal deficiency might have been responsible.

In Adult Females, Causing Changes Toward Adult Masculinity.—In the female after puberty and before the menopause, there occurs what has been called the adrenogenital syndrome. According to Wintersteiner, this in its broadest sense comprises all conditions in which the abnormal changes in the sexual sphere are referable to organic or functional disturbances in the adrenal cortex. In these females it consists of the appearance of male secondary sex characteristics and the repression of female characteristics and function. Apert called it "adrenal virilism." When the syndrome becomes established after puberty or in later life, hirsutism is the first change noted, followed by irregularity or cessation of the menses, changes in the body contour, and enlargement of the clitoris.

This type of syndrome is not infrequent. For the last fifteen years we have examined several hundred females showing some or all of its symptoms. From a study of these cases, the anatomic condition of the adrenal gland has often been found to bear no definite relation to the type or severity of the symptoms. The glands with the syndrome may be often grossly normal, slightly or considerably hyperplastic.

Tumor is not a frequent cause of the syndrome. When an adrenal cortical tumor is present with the syndrome, its complete removal is followed by the cessation of the syndrome with a return, all or in part, toward normal and is now considered to be definitely the cause of the syndrome. When tumor occurs, the first symptom has been scantiness of menstruation followed by cessation. When the menses cease, the cessation has been complete. Frequently headaches may occur at the time when menstruation should have occurred. Associated with the absence of menstruation has been a loss of sexual desire. Transfer of attraction to females has been described with return to normal opposite sex after removal of the tumor. Preceding the cessation of the menses or coincidental with or shortly afterward, there is a marked increase in the growth of hair on the face, chin, and body, all resembling the masculine distribution. Acne often occurs on face and chest. The voice frequently becomes deeper and masculine in tone.

Changes occur in the secondary sex organs, but this change is a slower one than that seen in the hair and menses. The younger the individual, the more pronounced are the secondary sex changes. The usual changes in the sexual organs are hypertrophy of the clitoris, deepening of the color of the labia, atrophy of the uterus, and atrophy and loss of sensitivity of the ovaries. In young females the breasts may stay undeveloped, resembling a boy at puberty. In older women atrophy may occur.

These changes have been shown to be associated with the appearance of excessive amounts of androgens in the urine. The amounts of androgens excreted are proportionate to the masculinity changes that have occurred. The amount may be far above that normally excreted

by males. From one of our cases, Gallagher reported 480 international units per day, and the average value for the normal male in his estimation was 40 international units per day. The highest recorded figure has been in the case described by Slot, in which the excretion reached the astounding figure of 2,200 international units per liter. The male hormone isolated from the urine in some of these tumor cases has been identified as dehydro-iso-androsterone.

Fig. 1.—Case of young woman with apparently only excess of male hormone produced by adrenal cortical tumor. Photograph before operation, showing one day's growth of beard.

There were two patients among the observed adrenal cases in which the only changes caused by the tumor could have been produced by excess androgens. They both had the amount of excretion estimated, the tumor diagnosed, located, and removed, with the disappearance of the male hormone in the urine following the removal of the tumor and the gradual return to normal of their secondary sex characteristics. Both of these cases were reported completely in 1942 (Cahill, Melicow, and Darby). One of these patients later had a reappearance of her syndrome with androgens in the urine, a tumor diagnosed in the opposite adrenal, identified as present by air-insufflation x-rays, and the tumor resected from the normal portion of the adrenal, followed again by the disappearance of the androgens in the urine and the gradual restoration of secondary sexual characteristics to the female.

These two cases presented tumors with secretion of marked excess androgens. The androgens in both produced masculinization, less in the

case with less hormones and marked in the case with excessive excretion. Removal of the tumors in each of these was not accompanied by acute adrenal deficiency, because with only excess androgens secreted there apparently was no functional atrophy of the opposite adrenal in excretion of life maintenance hormones. In one patient with ultimately bilateral tumors, a partial resection was done on each side.

In none of these tumors could a definite diagnosis of carcinoma be made. Pathologically they were thought to be adenoma.

Fig. 2.—Photograph of face taken after operation, with one day's growth of beard.

Changes in a Male Child Toward Adult Masculinity.—The usual syndrome described with adrenal cortical tumor in a male child has been that of precocious puberty. In very few cases tumors of the pineal gland have been responsible for sexual precocity in boys (Weinberger and Grant). There have been reported three patients as having the syndrome caused by testicular tumor (Sacchi, Moreau, and Parkes-Weber and Howland). A number of cases have been described in the literature as due to no known cause. Among these has been a description of its familial tendency without tumor by Rush, Bilderback, Slocum, and Rogers under the term macrogenitosoma. The occurrence of the syndrome as caused by adrenal cortical tumor is not frequent. Kepler states its frequency as twelve times among thirty-seven known adrenal tumors in children, a proportion of about two females with pseudopubertas praecox to one male with pubertas praecox.

Among the earlier cases was that reported by Linser, in 1903, of a boy 5 years of age with a left adrenal tumor with metastases. The sec-

ond was Adams, in 1905. Player and Lisser added one to the literature up to 1932, bringing the total to nine.

Cases of the syndrome must occur without reporting, either because of the marked advance of the disease before recognition, so that no operative procedure was undertaken, or because no autopsy was possible to prove the diagnosis. Broster and associates, in an exhaustive study of cases, recorded only one case of a male with prematurity. Fraser reported a case in 1941 in a child 1 year of age. From the few cases reported, the occurrence of premature puberty caused by adrenal tumor is among the rarer of adrenal tumor cases.

Fig. 3.—Photograph of woman with tumor producing male hormone and other metabolic hormones producing the Cushing-type syndrome.

We have studied five male children with prematurity, 5, 6, 8, 11, and 11 years of age. They all had hair on genitals and body, beginning on the face, and enlargement of the penis. The testes in the younger patients were not enlarged more than the normal age growth. The younger children showed more advanced age growth, advanced dentition, and epiphyseal development. They had no adiposity or other metabolic changes. There were no changes in sella, no evidence of pineal enlargement, and no changes in the thymus. One patient only showed an anatomic enlargement of one adrenal, the left, but this was not confirmed by operation.

The two older boys, 11 years of age, showed marked hirsutism of face and body and marked hypertrophy of the genitals, including the testes. Their symptoms had been present, one for eight and the other for seven years. There was shortening of the stature with fusion of epiphyses. Both had prostatic secretion and sperm. One had normal-sized adrenals by air-insufflation x-rays, and the other had an increase in size of the right adrenal. No operative procedures were done. These cases resembled the description of familial pubertas praecox described by Rush and associates.

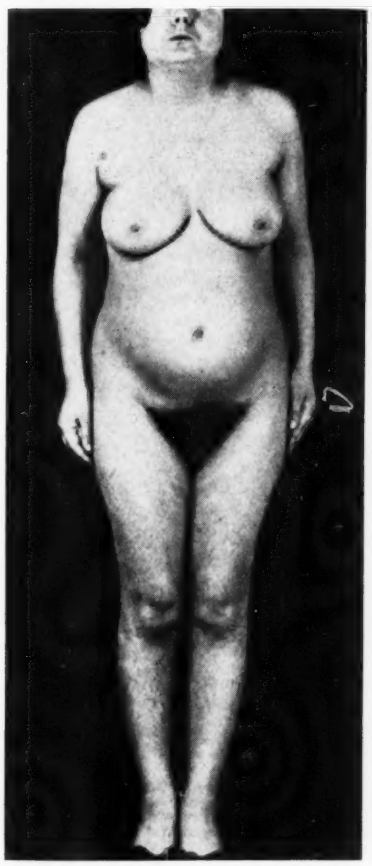


Fig. 4.—Photograph of woman with tumor producing only changes of metabolic hormones of the Cushing type. No female or male hormone was identified as excreted in her urine.

A case was seen in the terminal stage of a child of 5 years of age, with all the symptoms of the syndrome. This patient showed the facial and neck obesity as well as body obesity and genital hypertrophy described as the infant Hercules type. He had a large abdominal tumor, presumably adrenal. No pathologic specimen was obtainable.

The operative results reported on the few boys with the syndrome have had a very high mortality. In addition to the prematurity,

most obviously due to the effect of androgens, there appears very frequently symptoms suggestive of the changes seen with Cushing's syndrome and with probably a resulting functional atrophy of the opposite adrenal. In Fordyce and Evans' case, practically no adrenal tissue was found at autopsy on the opposite side. Player and Lisser's patient, who made the first surgical recovery in this group, showed only the androgenic effect in his masculine maturity and in his epiphyseal growth. He showed no evidence of acute adrenal deficiency following the removal of the tumor and made an uneventful recovery.

TUMORS WITH EXCESS ESTROGENS

Tumors with excess estrogens apparently are the rarest of all the hormonal tumors of the adrenal, only six definite cases of tumors with excess estrogens producing changes in the adult male toward femininity having been reported. The first was by Bittorf in 1919, a male, 26 years of age, who noticed decrease in the size of his testes and enlargement of his breasts. He became impotent and developed a tumor in the left side of his abdomen. Cachexia and death followed, and autopsy (Matthias) showed a "malignant adrenal cortical hypernephrome." Zum Busch reported a similar case with secretion from the patient's breasts and the cause verified by autopsy. Holl reported a patient, 15 years old, who was operated upon, the diagnosis established, but the tumor impossible to remove. He reported a second patient, 44 years old, with similar symptoms in which the tumor was removed by operation, followed by recovery. Following recovery there was a subsidence of breasts, adiposity, and return of sex function. Lisser published autopsy findings of a male, 33 years of age, with breast enlargement and secretion and adrenal cortical carcinoma. Simpson and Joll, in 1938, published an exhaustive investigation of a patient, aged 34 years, who had feminization due to an adrenal carcinoma and excreted an excess of estrogenic hormone (probably estrone). The excess of hormone disappeared after the operation and returned with the recurrence of the tumor in the form of metastases.

We have had one case, a man, aged 53 years, with gain in weight, increase in size of breasts, and changing of his hair to a finer, silkier type. He noticed a complete loss of desire and libido, with marked decrease in size of penis and testes. Perirenal air-insufflation x-rays showed a very large left adrenal. He permitted no further studies, and adrenal tumor was not verified, no operative procedure being done.

From the few cases in the literature and especially from the one reported by Simpson and Joll, the adrenal in these cases was directly responsible for the feminization and the adrenal cells were apparently the source of the estrogenic hormone. It was also shown by Simpson and Joll that androgens were still excreted by their patient.

Of the two reported patients with estrogenic tumors who recovered, in neither was removal of the tumor followed by acute adrenal deficiency.

TUMORS WITH SYMPTOMS DUE TO EXCESS ANDROGENS AND OTHER HORMONES

From a study of the literature, tumors with symptoms due to excess androgenics and other hormones seem to occur more frequently than any other. The symptoms without the cause being tumor are not infrequent. In the large number of supposed adrenal cases referred to us, this type of adrenogenital syndrome was frequent. Our studies of these showed that a fair number of these patients had hypertrophy of one or both adrenals. Few, however, had tumors as causation.

Fig. 5.—Hypertrophy of the clitoris in female child with masculine stature due to excess androgens elaborated by adrenal adenoma.

The syndrome as described by Cushing was followed with the suggestion that it occurred with basophilic adenoma of the pituitary. He outlined a clinical picture consisting of a rapid, plethoric, painful obesity, affecting primarily the face, neck, and abdomen, but usually sparing the limbs, thus giving rise to an obesity described as the "buffalo type." The facial changes made the eyes appear small and slitlike, resembling a pig's eye. There was acrocyanosis, with purplish, linear atrophiae on the lower abdomen and the thighs. Hirsutes were marked. There was a tendency toward polycythemia and hypertension, and glycosuria was of frequent occurrence, as were high cholesterol readings. With the syndrome were muscular weakness and porosis of

the bones, causing a cervicodorsal stoop and a shortening of the stature. This latter is rare in adrenal tumors, but more frequent with the pituitary cases. Amenorrhea was present in the females and impotence in the males. There was a marked susceptibility to infectious processes and to physical stress. Mental changes were present, and, in some, well-developed psychoses occurred.

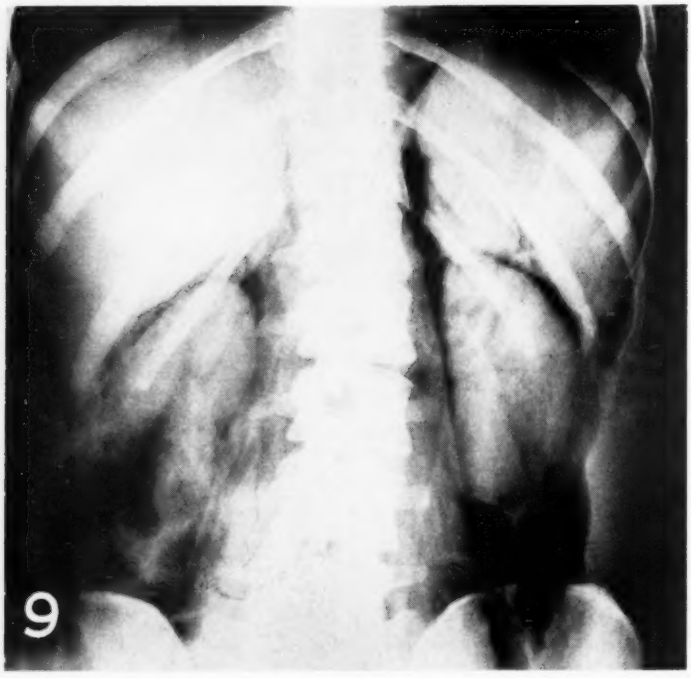


Fig. 6.—Air-insufflated x-ray of young woman with only masculine syndrome. An ovoid tumor of left adrenal is outlined above the kidney.

Since the description by Cushing, many reports have been issued as to the findings in these cases in which opinions have varied as to the causation. Some (Pardee) believe it mostly pituitary. Others reported that it was more frequently associated with adrenal changes (Oppenheimer and Silver, etc.). Some similar syndromes have been reported as having been associated with thymic tumors. A few rare cases with obesity and hirsutes, as well as hypertension, have occurred with the arrhenoblastomas described by Robert Meyer.

From a study of these cases, some of the changes could be due to the effects of excess androgens. These changes were the hirsutes, amenorrhea, and changes in the secondary sex organs, as the breasts and the clitoris. Some patients had these changes to a marked degree and others less. The fat deposits, the skin, polycythemia, hypertension, and glycosuria, as well as the weakness and osteoporosis, can best be explained by excess hormones present, disorganizing such metabolic processes. Bauer

called attention to the fact that these, in their main effects, were the opposite to Addison's disease, and that most of these individuals were suffering from an excess of metabolism steroids produced by the adrenal, either by itself or through stimulation of the pituitary. Considerable support to this has been offered by clinical observers and by investigators.

Tumor of the adrenal has definitely been shown to be a producer of most of the changes in this syndrome. When tumor occurs, the cases may vary from those with marked sex changes and mild other metabolic changes to those with less marked sexual changes and most of those described by Cushing.

Fig. 7.—Photograph of tumor removed from patient shown in Fig. 6.

We studied and reported three cases (Cahill, Melicow, and Darby) showing these variations. The first, a woman, aged 36 years, had hirsutism, amenorrhea, stoutness, nervousness, and weakness. There was hypertrophy of the clitoris and a mild erythrocytosis. Air-insufflation x-rays of the adrenal showed a large tumor of the right with a small opposite adrenal. She excreted 69 international units of male hormones each day. The right adrenal tumor was removed successfully. Following this removal she developed acute adrenal deficiency and died thirty-six hours later. The second case, a woman, aged 36 years, had weakness, headaches, hirsutes, amenorrhea, edema, acne, erythrocytosis, low sugar tolerance, and hypertension. A larger tumor of the adrenal was shown by perirenal air insufflation. Removal of this by operation was followed by acute adrenal deficiency, but she recovered with

vigorous therapy. After recovery her normal female characteristics returned, only to be replaced again later by masculinization and more marked other metabolic changes with growth of metastases, from which she died. The third woman, aged forty years, had hirsutes, fat on face and body, emaciation of limbs, and amenorrhea. Study showed erythrocytosis, low sugar tolerance, and hypertension. She developed cervicodorsal stoop. Air-insufflation x-rays showed a large tumor of the adrenal. No operation was performed, and follow-up was impossible.

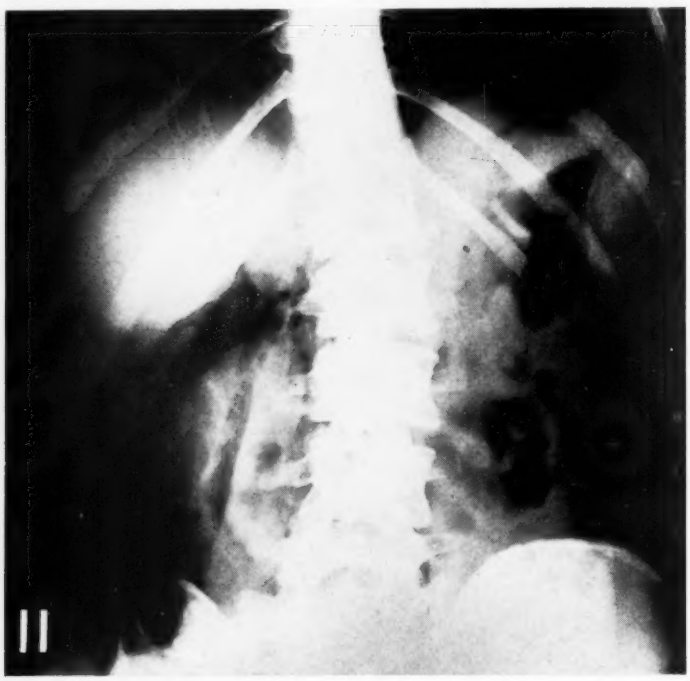


Fig. 8.—Air-insufflation x-ray showing tumor of lower pole of the right adrenal in a patient with only masculinizing syndrome.

The three cases studied appear to be illustrative of the variations caused by the effect of different hormones. The first had well-marked effects of excess androgens and moderate other metabolic disturbances. The second had well-marked sexual changes and other metabolic changes. The last had moderate sexual changes and marked general metabolic changes. In these the demonstration of the tumors by air insufflation was less clearly defined, as the patient developed fatty deposits and edema. The operative results show that apparently, with the excess of metabolic hormones produced by the tumor, hypofunction and atrophy occur in the opposite adrenal. This fact has been reported by other observers. Often when one of these patients recovers it may be due to the excretion of hormones by metastases.

TUMORS WITH CHANGES DUE TO EXCESS OTHER STEROIDS RELATED TO METABOLISM

We had one patient previously reported who had all the symptoms described by Cushing with the only real change in the sexual characteristics being the cessation of menstruation. No male or female hormones could be identified as excreted in her urine. A complete autopsy was done after she died with acute adrenal deficiency after removal of the adrenal tumor; this did not reveal any other change that could have produced the syndrome except the adrenal tumor. The remaining

Fig. 9.—Photograph of tumor removed from patient in Fig. 8.

adrenal was atrophic and apparently inactive. In retrospect the tumor must have produced steroids in abundance, as was evidenced by the histologic sections, in which most of the cells were foamy with lipoids. These steroids were neither of androgenic nor estrogenic influence, as was shown by the symptoms and by the failure to identify either in the urine. From her symptoms and the fact that acute death followed the removal of the tumor, the steroids apparently had to do with the life maintenance properties of the adrenal.

THE DIAGNOSIS OF ADRENAL CORTICAL TUMORS WITH HORMONAL EXCRETION

From a study of many cases with syndromes suggestive of adrenal changes, only rarely have we found tumor as the cause. When tumor

occurs the symptoms are usually pronounced. If of androgenic character, the identification of large amounts of androgens in the urine is necessary. This is now possible by the estimation of the 17 ketosteroids by the colorimetric method. If the symptoms are of estrogenic character, the estimation of the urinary estrogens biologically is not difficult. Once these excesses are determined, the origin of the hormones is then sought. For the adrenals we have used x-ray studies of air insufflated into the perirenal fascial spaces. These have been reported by us and

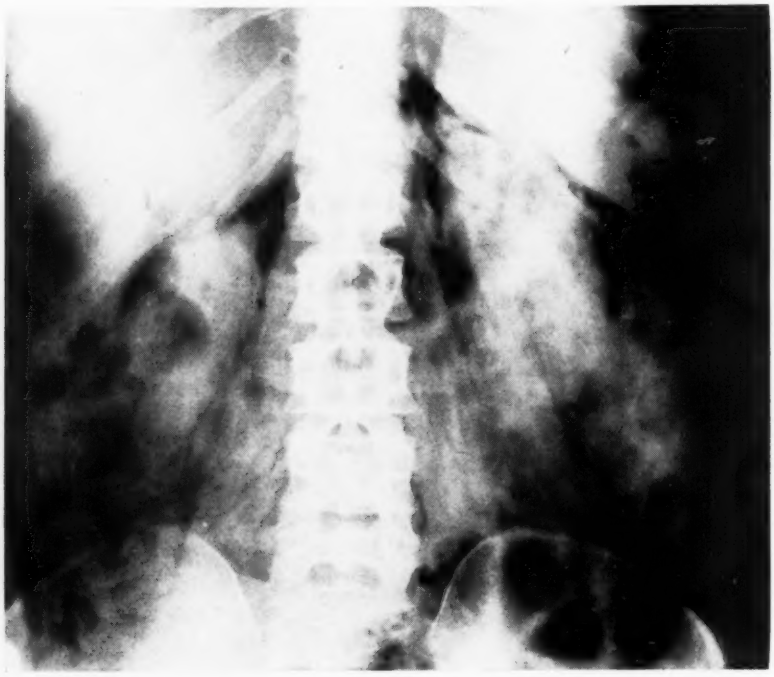


Fig. 10.—Air-insufflation x-ray showing tumor of the right adrenal resting against the liver in a patient with masculine syndrome and Cushing syndrome.

others. When tumor is present, it is more clearly shown in thin people. The tumors are round when small, ovoid when large, and may be somewhat lobulated when very large. All tumors so diagnosed were confirmed by operation. The air insufflation was especially of value when the tumor was small and unrecognizable by any other method except by operation.

THE HORMONES EXCRETED BY ADRENAL CORTICAL TUMORS

Androgens.—It is apparently established that virilism and adrenal cortical tumors, when present, are associated with high levels of androgen, and this declines to lower levels after removal of the tumor. The most frequent androgen that has been isolated has been shown to be dehydro-iso-androsterone, a beta-kesteroid. This differs from the hormone of the testes, testosterone, an alpha-kesteroid. It is also thought

that the adrenal may also produce some alpha-kesteroids. Under certain conditions the beta-kesteroids are greatly increased in quantity, as in patients with hyperplasia, adenoma, and carcinoma of the adrenal cortex. In these cases there appears to be a rather definite relation of the amounts of androgens present in the urine to the degree of virilism. The more marked the symptoms, the higher the assay.

It has been shown that at least with one tumor another kesteroid (pregnane) was isolated from the urine by Butler and Marrian and appeared to be associated particularly with that tumor; it was not found in the urine of either normal males or females or of pregnant females. From their finding it appears as if in other tumor cases abnormal or perverted hormones may be elaborated.

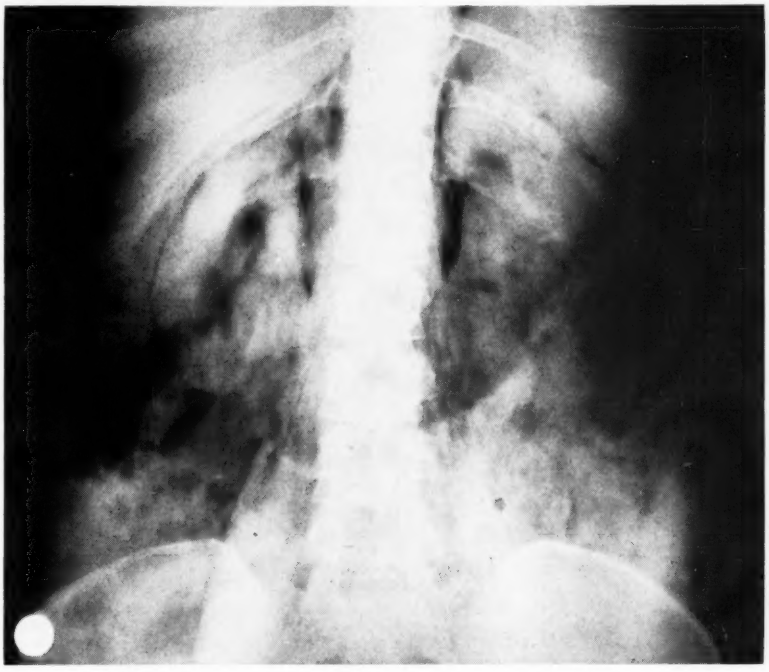


Fig. 11.—Air-insufflation x-ray showing tumor of the left adrenal in a case of only metabolic changes of Cushing type. The air diffuses poorly around this adrenal due to fatty edema of the tissues.

Esterogens.—It was shown early that large amounts of estrogens were excreted in the urine of patients with virilism and tumor. In some a definite excess over normal was found, even though the effect on the patient was masculinization. At that time the amount of androgens was unknown. Later we have shown, as well as others, that even though the androgen level is greatly in excess of normal, high estrogen excretions continue in women with adrenal cortical tumors with masculinizing syndromes; and these estrogens remain unchanged after the tumor is removed.

The report of Simpson and Joll confirmed the clinical suspicion that feminizing tumors in males must be associated with high estrogen levels. Their case showed high levels before operation, lowering to normal after removal of the tumor and resumption of high levels again with the reappearance of tumor in the form of metastasis. The estrogens excreted in their case were considered to be estrone.

OTHER HORMONES

The identification of other hormones with adrenal cortical tumors awaits further investigation. An increase in substance which maintains life was demonstrated in the blood stream of a patient with Cushing's syndrome. The identification of life-maintaining substances in the urine

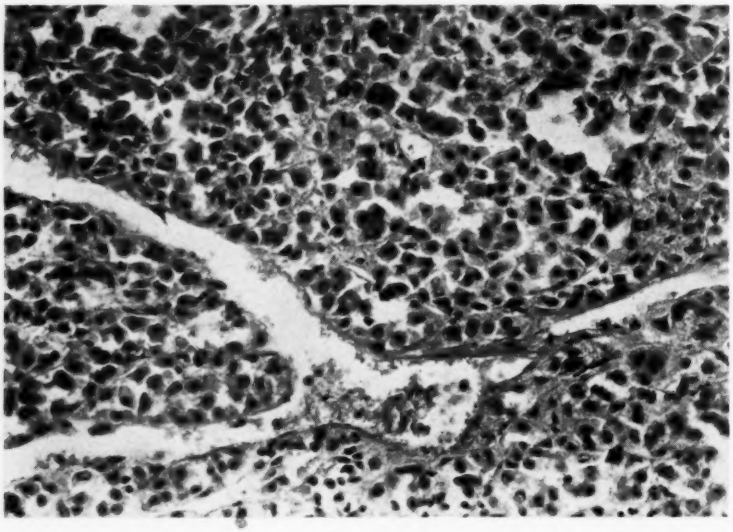


Fig. 12.—Photomicrograph of tumor of adrenal cortex with only masculinizing syndromes.

in normal persons and their increase in stress has been reported by Weil and Browne. Similar investigation into the excretions of the Cushing syndrome types is needed. Of particular interest was the patient with Cushing's syndrome, in whose urine neither androgens nor estrogens could be identified.

OPERATIVE PROCEDURES

For removal of adrenal cortical tumors, three routes of approach have been used: (1) extraperitoneally through the lumbar region; (2) transthoracically through the diaphragm; (3) transperitoneally through the anterior abdominal wall.

The lumbar route has been used extensively for adrenal surgery that did not involve tumor removal. Crile used this method in his adrenal approach. Walters and Kepler reported doing bilateral exposures to

determine, first, the diseased side, and, second, the presence of an opposite adrenal. Young devised an ingenious retractor fashioned after a rib-spreader retractor for thoracic procedures and used this retractor for bilateral exposure.

The transthoracic approach was reported by Broster and Vines as useful in cases of nontumor adrenogenital syndrome. This, he claimed, was the easiest approach in view of the fact that the adrenal vessels allowed a slight range of upward movement. It had, however, the disadvantage of creating at times a pneumothorax. He also did a preliminary laparotomy for exploration of the adrenals by palpation, then after recovery performed the main operation by the transthoracic approach.

The transperitoneal approach has been used in association with a bridge elevation similar to gall bladder procedures. This approach we have recommended for cortical tumors because we have felt that,

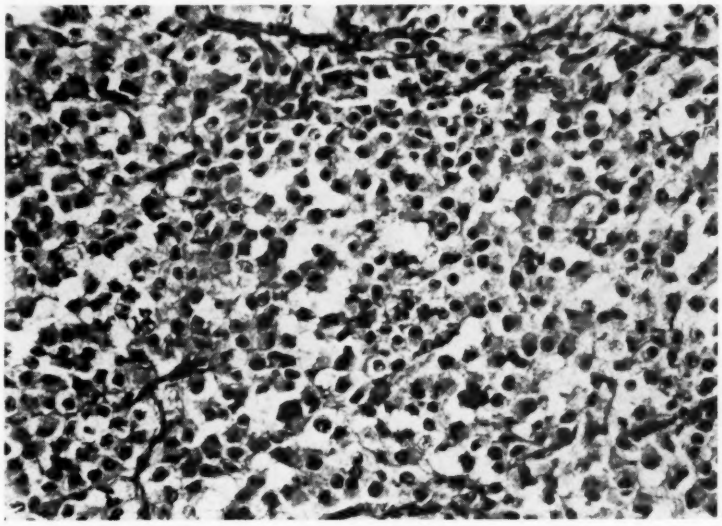


Fig. 13.—Photomicrograph of tumor of adrenal cortex with mixed syndromes. The cells contain many vacuoles of steroids.

with the adrenal, in both the lumbar and transthoracic routes the operator was too handicapped with the inadequacy of the incision, the difficulty of first approaching the vessels of the tumor and of ligating them, and the difficulty of manipulating the tumor. The anterior oblique incision gives a large opening, adequate exposure, exploration of the entire abdomen, proper localization of the structures, accessibility to the tumor which always grows down and anteriorly in the direction of the incision, and ability to ligate the vessels before handling the tumor, a most recommended step in dealing with carcinoma and facilitated by far better control of any operative accident. In our series there have been no weaknesses in the abdominal wall subsequent to the operation.

POSTOPERATIVE ACUTE ADRENAL DEFICIENCY

In the literature many patients are reported with what has been described as shock, occurring immediately or shortly following the removal of an adrenal tumor. Cecil stated that 39 per cent died of this shock and that 65 per cent had severe shock, from which only 27 per cent of all patients operated upon recovered. The other 33 per cent apparently had no shock.

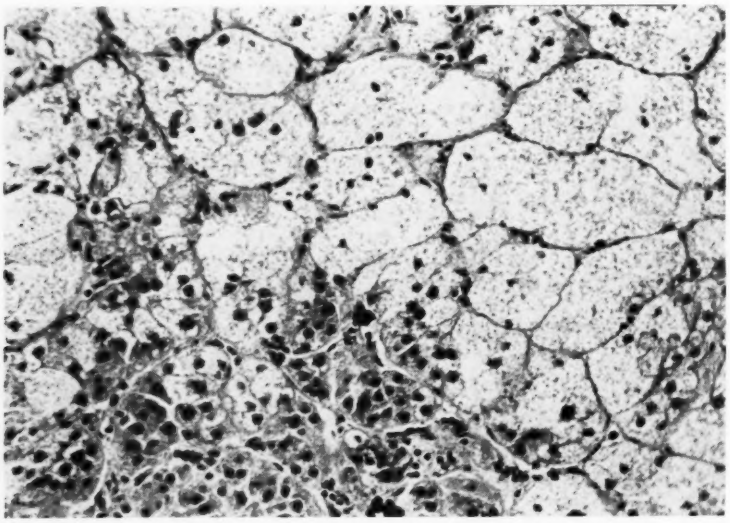


Fig. 14.—Photomicrograph of tumor of adrenal cortex with only metabolic syndromes of Cushing type. Most of the cells are filled with vacuoles.

It is now accepted by most clinicians and investigators that the collapse is characteristic of acute adrenal deficiency. From a perusal of the literature and from our own experience, the acute adrenal deficiency is rare or does not occur in the nonhormonal adrenal cortical tumor cases, nor does it occur in those with only sex hormonal changes, but it occurs most often in those who show the effects of excess hormonal action upon many metabolic factors, the electrolytes, the water and salt balance, and the capillary permeability, in fact, the symptoms seen in the Cushing type of syndrome, whether in children or adults. It has been suggested upon reasonable grounds that these changes can only be produced by excess hormones. Experimentally it has been shown that injections of excess life-maintenance substance can cause atrophy of the adrenals. In those cases ending fatally, usually of the Cushing type of tumor, contra-adrenal atrophy usually is present. Cushing type tumors have been removed, and the patient has recovered from the following acute adrenal deficiency, but often metastases were later recognized; it is thought that their secretion was responsible for the recovery.

The most important factor in surgical therapy in these metabolic-type tumors is the anticipation, prevention, and control of postoperative cortical deficiency. The method used is that with acute crisis of Addison's disease, having on hand and administering preoperatively and postoperatively potent adrenal hormone. A potent extract of the cortex may be used or the synthetic hormone desoxycorticosterone. Adequate doses are given. In addition to the hormone there is administered by oral or parenteral route adequate amounts of sodium chloride and sodium citrate. Since the marked cases of Cushing syndrome have an erythrocythemia, with apparently a marked diminished blood volume, postoperative transfusions are often necessary. Certain students of the syndrome suggest that a diet low in potassium might be of value for some time preceding the operation.

If the patient is tided over the acute deficiency, it is expected that the remaining adrenal tissue will regain its capacity to produce a sufficient amount of hormone to meet the needs of the body. There apparently is no known method to determine the duration of this period, but it probably is safer to err on the side of extension of the therapy for some time after the blood pressure and electrolyte balance have reached normal.

PATHOLOGY

The tumors were either adenoma or carcinoma. The adenomas were soft, encapsulated, red tumors. The small ones blended into normal adrenal tissue. With larger ones, no normal tissue was found. The adenomas were more frequent in the younger adults. The cells were typical active adrenal cells, undistinguishable as coming from any particular zone. They at times had granules but contained lipoid vacuoles in many cells. The number of cells containing vacuoles compared roughly with the degree of hormonal changes, particularly if the Cushing type of syndrome was present; in this latter the sections of the slides showed that most of the tumors were composed of "foam cells."

The carcinomas varied. These were seen more often in the older cases. None of the carcinomas resembled those seen in adrenal tumors without hormonal syndromes. One carcinoma showed invasion of the capsule and cells in the blood vessels. The cells were in sheets resembling some parts of the adrenal cortex, more frequently the glomerular and reticulate layers. Numerous vacuoles were present. Others had cells mostly undifferentiated with many mitoses and numerous vacuoles.

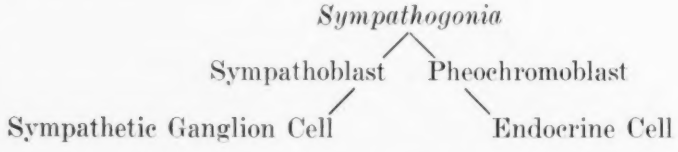
The attempts to correlate the findings of fuchsinophile granules as described by Broster and Vines have still left us unable to decide whether their presence has or has not any particular association with the various types of cases. Fuchsinophile staining of the cytoplasm was present in all the tumors, in some diffusely and in others in gran-

ules. It apparently was more pronounced in cases with hormonal syndromes and in the older individuals. The latter is in accord with Sudds' report that granules appear in adrenal cells, apparently with the ageing process of the individual.

HORMONAL TUMORS OF THE ADRENAL MEDULLA

Tumors of the adrenal medulla may be divided clinically into those which produce no hormones and those which do. The latter are rare.

The medulla of the adrenal is of the sympathetic nerve system. The cells are formed from the sympathogonia which grow into the cavity of the adrenal cortex, which gradually extends over the medulla to enclose the same. The primitive sympathetic cell (sympathogonia) forms two types of cells, one the fibril ganglion cell, and the other the secreting endocrine cell. The former, the sympathoblast, forms the mature sympathetic ganglion cell, and the latter, the pheochromoblast, forms the mature pheochromocyte.



The pheochromocyte cell is the mature and apparently only endocrine secreting cell of the adrenal medulla. Long before the present knowledge of its function was known, it had been shown to possess an affinity to chrome salts which stained material in its cells a deep brown. Cells with similar staining properties (chromaffin tissue) occur in the retroperitoneal tissues, sympathetic glands along the aorta, Zuckerkandl's organ, the sacrococcygeal region body, and the carotid body.

The only known secretion of the pheochrome cell is epinephrine. This was the first hormone identified, isolated, and synthesized. Its properties as a pressure substance have long been recognized.

When there is an abnormal number of pheochrome cells produced, as in tumor, the formation of such has been called paraganglioma chromaffinoma, or, more properly, pheochromocytoma. The symptoms of paroxysmal hypertension now known to be associated with pheochromocytoma were first described, in 1922, by Labbé and Tinel-Doumer. The diagnosis as to its causation was made, in 1926, by Vaquez and Donzelot. C. H. Mayo reported, in 1927, the first pheochromocytoma removed during an abdominal exploration. In 1929, Pincoffs reported the first case correctly diagnosed and the patient operated upon. The association of the pressor substance in the blood with the attacks was first reported, in 1937, by Beer, King, and Prinzmetal.

When pheochromocytoma occurs, it is more frequent in the medulla of the adrenal gland, but it may occur next in frequency in the retro-

perintoneal tissue, in the ganglia with the aorta or vena cava, in the sacrococcygeal body, or in the carotid body. When the tumors are small, they are usually soft, reddish tumors with a thin capsule, and usually the adrenal cortex is a yellow rim attached to the tumor. When larger, they become grayish or darker brown. They are vascular and easily ruptured. Hemorrhage and degeneration are not infrequent. Cyst formation may occur.

When the tumor occurs, a symptom complex is seen, which gives rise to what has been described as paroxysmal hypertension. The course has been accepted as being the effect of a release of an excess amount of pressor substances in the blood.

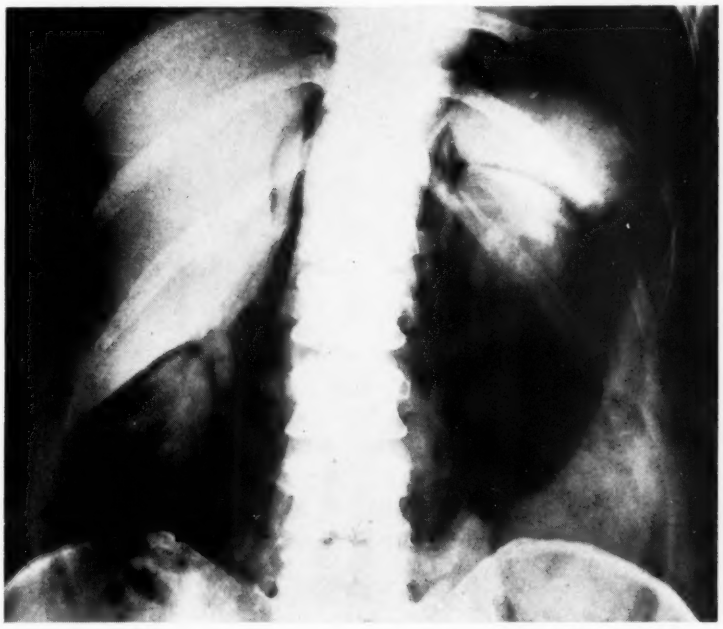


Fig. 15.—Air-insufflation x-ray of patient with pheochromocytoma of the right adrenal.

The tumors so far occur usually in young or middle adult life and in both sexes, although they apparently are more frequent in the female. They are more often benign, and the patient in the rare malignant case may succumb before many metastases occur.

THE SYNDROME

The symptoms that occur have been described as paroxysmal hypertension. These may occur spontaneously or may be induced. When they occur they usually are similar each time.

The patient notices that after exercise or mental excitement a marked pounding headache occurs, with the consciousness of the heart beating; that there is tingling of hands and feet with a feeling of constriction of the same and creepy feelings; that palpitation becomes more marked; that dyspnea may occur with nausea or vomiting; and that at

times epigastric pain is marked. An impending sense of death not infrequently occurs. The attacks last from a few minutes to several hours, and in that time the patient may simulate a state of shock. The attacks terminate slowly with flushing of the blanched areas, marked sweating and weakness, and often exhaustion. Death may occur during an attack, from shock, heart failure, coronary disease, cerebral accident, or pulmonary edema. Frequent occurrence of the syndrome may result in arterial changes, in which a more or less continuous hypertension may exist with vascular changes in the eyes.

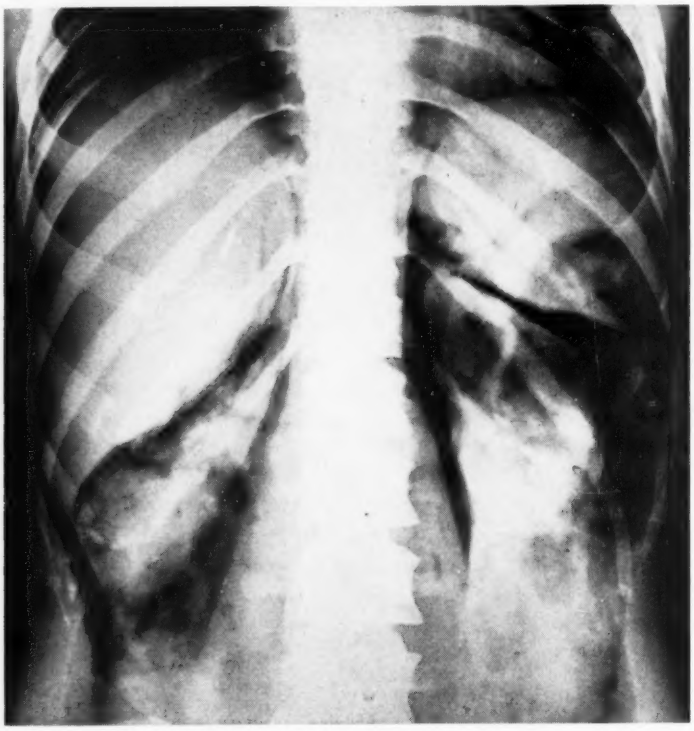


Fig. 16.—Air-insufflation x-ray of patient with small pheochromocytoma of the lower pole of right adrenal.

CAUSATION OF ATTACKS

The attacks may be produced spontaneously or by physical or mental effort. They have been variously described, often being attributed to other causes. Any mechanism that is known to release adrenalin normally from the adrenal may produce the attack, as effort, trauma, anger, fear, exposure to cold or sudden heat, abdominal pressure, massage of the tumor, or, accidentally, administration of a pressure substance. Some patients have awakened from sleep with an attack, probably from dreaming. Not uncommonly, as in several of our cases, the sudden demise in an unrecognized tumor followed by an autopsy discloses the cause.

VASOCONSTRICTION

The vasoconstriction of the peripheral circulation is usually marked. The blood pressure between attacks may be low or normal. During the attack it may rise to over 300 mg. systolic with a diastolic over 100 mg. of mercury. The pulse is thin and may not be perceptible. The fingers and toes become blanched, as well as the lips and also the fundus oculi. There occurs a difference of pressure reading in the proximal arteries from the distal arteries. Readings by oscillograph may not be possible in the extremities. During this period the pulse is rapid, and the heart pounding may be pronounced.

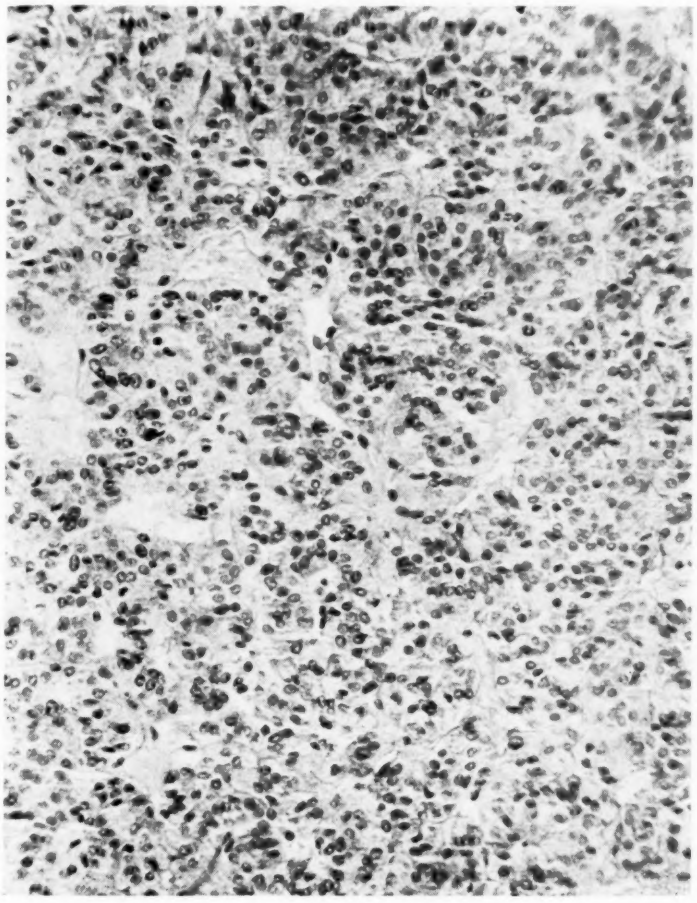


Fig. 17.—Photomicrograph of pheochromocytoma taken from patient shown in Fig. 15.

Temperature.—There is a marked diminution of the peripheral temperature of the body with a rise of the internal temperature. This persists through the attack, evidently produced by inadequate dissipation of body heat. Following the attack, subnormal temperature may be present for a while.

Shock.—Following a severe attack or one which has existed a long time, a state of shock may occur. Similar phenomena have been re-

ported experimentally in animals by continuous introduction of epinephrine. The shock may be fatal with the anemia that follows the marked dilation of the blood vessels and with acute plasma loss.

Urine.—During the attack a sugar tolerance test usually resembles that seen in diabetes. The blood, however, shows an increase in sugar during the attack, evidently from increased liver function. The urine during an attack is usually decreased in volume, usually contains albumin and casts. Red blood cells are often present. The urine in such individuals may be normal between attacks.

Blood.—Usually because of the necessity of avoiding exercise, most patients have a mild anemia. During the attacks the presence of pressure substances was first demonstrated by Beer, King, and Prinzmetal. This they showed by the effect produced by perfusion of a denervated rabbit's ear, using a modification of the Pissemski method. They compared the result with a control and showed the marked pressor effect with the blood during an attack. They also were able to demonstrate a reversal effect with ergotamine tartrate. They believed that the pressure substance was certainly adrenalin.

During the attack there has also been shown to occur a lowering of the blood sugar content.

Electrocardiogram studies have shown during the attack a left preponderance which subsided to normal for the individual between attacks.

DIAGNOSIS

The definite diagnosis of pheochromocytoma depends upon:

1. A typical attack and associated clinical findings
2. Clinical evidence that the attacks are produced by a pressor substance
3. Demonstration in the blood of a pressor substance and disappearance in the demonstration of the pressor effects by ergotamine
4. Roentgenographic evidence of the presence of a tumor by perirenal insufflation

Hypertension under certain circumstances, particularly in the presence of exposure to heat or sun, may simulate the attacks of adrenal pheochromocytoma. Coronary occlusion may resemble the same, although hypertension of the type with adrenal tumor is not frequent. When first seen, acute hyperthyroidism may be difficult to differentiate from these adrenal attacks. Hysteria in a person familiar with the syndrome caused a false syndrome that could be disproved only by complete operative exploration which revealed no evidence of tumor.

THERAPY

Preoperation.—Emotional stress should be avoided. No discussion with the patient of any of the procedure will be best; in fact, a basal

avertin anesthesia should be administered before any of the preparations, as shaving, are commenced. Adrenalin and adrenal cortical hormone should be available, as well as adequate salt therapy, because depletion of both hormones after removal may leave the patient in collapse. In one of our cases of pheochromocytoma associated with an adrenogenital syndrome, the patient suffered from an acute adrenal cortical deficiency.

Operation.—The blood pressure readings should be taken as frequently as possible. For small tumors a large lumbar exposure may offer adequate space so that the tumor may be removed with as little handling as possible. If large, the oblique transperitoneal incision is best, because of the larger exposure and because ligation of the vessels first, before the tumor is handled, is possible through this incision. If the tumor is handled little, the rise in blood pressure noted may be moderate. If the tumor is traumatized, the pressure rise may be striking and at times fatal. Following removal of the tumor the blood pressure falls, and this may require adrenalin or adrenal cortical extract. The tumors are very soft, and the capsule is easily ruptured. If this occurs, fixation of all the loose cells may be done with 70 per cent alcohol and then sponged out with warm saline solution.

Postoperative Care.—Combating of the postoperative depleted state may be by intravenous infusion, adrenalin, or adrenal cortical extract. The patient rapidly returns to normal if the collapse is overcome. Few of the patients have a continuous low blood pressure for months. A recurrence of the syndrome has been reported after removal of a tumor successfully. This has been thought to be a new tumor in some other pheochrome tissue elsewhere.

We have available reports of nine patients with pheochromocytoma who were hospitalized at the Columbia Presbyterian Center. There were several other cases in which the syndrome was suspected, operative procedures performed, but no tumor demonstrated.

CASE 1 (P. H. No. 59936).—In 1924, J. B., a man aged 59 years, was admitted with a fracture of the ankle. He gave a history of some serious attacks, which he called liver attacks, which left him prostrate. The occurrence of one of these attacks after reduction of the fracture was thought to be due to a coronary occlusion or thrombosis. One medical observer called attention to the very marked elevation of the blood pressure as unusual with a severe coronary attack. The attack was fatal. Autopsy showed no coronary disease, but a malignant pheochromocytoma was found with metastases to the liver and lymph glands. At that time its association with the attack and death was not correlated.

CASE 2 (P. H. No. 312177).—In 1932, E. W., a blind man, aged 33 years, was admitted with weakness and wasting of the right leg and arm, and he was seriously ill with nausea, vomiting, and collapse. Death occurred, and autopsy showed multiple liposarcoma of the spinal cord as the cause of the paralysis of the extremities and a large, benign pheochromocytoma of the left adrenal as the presumptive cause of collapse. Previous history had shown attack similar to syndromal adrenal hypersecretion.

CASE 3 (P. H., No. 438208).—S. P., a woman aged 53 years, was admitted in 1934; she had had so-called attacks of chronic indigestion for years. These were severe with epigastric pain, nausea, vomiting, and often collapse. The attack which brought her to the hospital was the most severe that she had ever had. A presumptive diagnosis of visceral perforation was made. Operation disclosed severe intraperitoneal hemorrhage from a mass above the right kidney. Attempts to control the hemorrhage were difficult, and the patient collapsed and expired. Autopsy showed that the hemorrhage was from a large, benign pheochromocytoma of the right adrenal, and death followed the attempts to control the hemorrhage.

CASE 4 (P. H. No. 542008).—D. P., a female, aged 27 years, was admitted in 1938; she had had a rheumatic heart for years and attacks of abdominal distress and palpitation. She had had an unsuccessful laparotomy eight years previously. She showed a typical syndrome of paroxysmal hypertension and had a palpable tumor mass in the left hypochondrium. Palpation and massage of the tumor mass produced the typical attacks. A partial removal of the tumor, which was attached to the cava and aorta, was followed by collapse and death. Autopsy showed severe rheumatic endocardial changes, marked arteriosclerosis, and a pathologically benign pheochromocytoma of the left aortic lumbar plexus.

CASE 5 (Neurological Institute No. 41024).—G. K., a man aged 61 years, was admitted in 1939. He had evidence of personality changes and had convulsive attacks. A diagnosis of brain tumor was made, and at operation a tumor was removed. Five days following the operation he died in a sudden collapse. Autopsy showed severe intraperitoneal hemorrhage from a pheochromocytoma of the right adrenal. The tumor removed from the meninges was diagnosed on microscopic examination as pheochromocytoma. There were no other metastases found.

CASE 6 (P. H. No. 600888).—E. C., a woman aged 49 years, was admitted in 1940 with a history of the typical syndrome of pheochromocytoma. The tumor was localized as in the right adrenal by air-insufflation x-rays. She was operated upon, the tumor removed from the adjacent cortex, and she made an excellent recovery and has been well since. The tumor was a benign pheochromocytoma.

CASE 7 (P. H. No. 657128).—J. S., a woman aged 48 years, was admitted in 1941 with hirsutism, obesity, and amenorrhea which had been present for years. One year before, the left adrenal had been explored in another hospital with no tumor found and the symptoms persisting unchanged. A tumor of the right adrenal was shown by air-insufflation x-rays. The tumor was removed by resection from the cortical portion because of symptoms of adrenogenital syndrome and because of the uncertainty of the status of the left adrenal after the previous operation. The tumor was shown microscopically to be a benign pheochromocytoma, but a removed portion of the cortex showed adrenal hyperplasia with many foam cells seen often with the Cushing type. An acute cortical adrenal deficiency following was treated by cortical hormone and she recovered. The patient has been free from the hypertension syndrome since the operation.

CASE 8 (P. H. No. 690134).—E. R., a female, aged 29 years, was admitted in 1942. For one year she had had attacks of paroxysmal hypertension. Studies did not reveal any changes in the adrenal, but there was a tumor mass below and mesial to the right kidney. Operation disclosed a tumor of the right aortic lumbar plexus. The tumor was removed. It was a benign pheochromocytoma. There has been no recurrence of the syndrome since operation.

CASE 9 (P. H. No. 623060).—H. A., a female, aged 25 years, was admitted in 1943, with hirsutism, mild obesity, and scanty menses. For one year she had had

typical syndromal attacks of paroxysmal hypertension. Insufflation x-rays showed a small bulbous mass at the lower pole of the right adrenal similar to that in Case 6. She refused operative intervention.

These nine cases cover the historical study of these tumors: The early case with an entirely unrecognized syndrome; the marked tendency of these tumors, particularly the right, to bleed intraperitoneally; the collapse and death that may occur with any traumatism; with hemorrhage from the gland, and with operative handling; the later recognition of the syndrome, with proper diagnosis, proper localization of the tumor, and its successful removal. Of the nine tumors, two metastasized and were thus presumed to be malignant.

SUMMARY

Cortical Hormonal Tumors.—

1. The hormonal syndromes may be due to an excess of androgens or estrogens or other metabolic hormones of the cortex.

2. The syndromes are determined by the type and amount of hormone or hormones produced and by the age and sex of the patient.

3. The status of the adrenals may be adequately determined by air-insufflation x-ray pictures.

4. Removal of the tumor, if adenoma, will cure the syndrome, but often fixed changes will persist. If the tumor is carcinomatus, its removal may temporarily improve the patient.

5. Acute adrenal deficiency occurs usually in those with symptoms of the Cushing syndrome, and the treatment is that of acute deficiency in Addison's disease.

Medullary Hormonal Tumors.—

1. The hormonal syndromes are due to an excess of epinephrine.

2. The cases vary only in degree with the amount of the hormone produced.

3. The diagnosis is made upon:

(a) a typical syndrome and response

(b) demonstration of a pressure substance

(c) the presence of tumor by air-insufflation x-ray pictures

4. The danger period is during the operation, although at times acute adrenal deficiency may develop from removal of cortical tissue.

5. If patients survive the operative period, the prognosis is good, because most of the tumors are benign.

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THE ENDOCRINE ACTIVITY OF THYROID TUMORS AND THE INFLUENCE OF THE THYROID HORMONE ON TUMORS IN GENERAL

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THE relation of the thyroid to new growth has been under investigation for some time, but the results have been rather inconclusive. The problem may be divided into two main categories, namely, the effect of thyroid hormone on malignant tumors in general and the effect of thyroid neoplasms on hormone production.

THYROID HORMONE VERSUS NEW GROWTHS

The chief function of the thyroid gland is the elaboration and storage of its hormone, thyroglobulin. This iodine-containing protein plays a vital role in the economy of the body. It regulates the rate of energy exchange, or metabolism. In addition, it has numerous other actions which are probably interrelated and dependent upon the main one, the calorigenic action. The thyroid affects growth, maturation and differentiation of tissues, the distribution of water, salts, and colloids in the body, the metabolism of carbohydrates, and the function of the neuromuscular and circulatory systems. It has some effects which are not clearly understood, such as the fluctuation in cholesterol metabolism, tolerance to certain drugs, absorption from the gastrointestinal tract, motility of the gastrointestinal tract, and the formation of blood. The function of the thyroid is still further complicated by its direct and indirect effect on the other endocrine glands, which, in turn, act upon the thyroid. The physiologic action of thyroid is best illustrated in the two clinical conditions of exophthalmic goiter and myxedema or cretinism. In the one, the manifestations of the disease, except for the eye signs, are due to excess secretion of thyroid; in the other they are due to undersecretion of thyroid.

In view of the profound effect that thyroid has on normal tissues, it has been assumed that this hormone would also affect the development and growth of abnormal tissues, such as neoplasms. A great deal of work has been done on this subject. Most of the results indicate that the state of thyroid function is not important in experimental tumors. Thyroxine has no influence on the incidence and growth of various types of transplantable mouse tumors (Sugiura and Benedict,[1] Salter, Nathanson, and Wilson[2]) or on rate of sarcoma production in

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chickens (Okamura and Namiki[3]); thyroidectomy also is without effect on such tumors (Bischoff and Maxwell[4]). In the case of chemically induced tumors, the recent report of Smith, Wells, and D'Amour[5] indicates that neither thyroid administration nor thyroidectomy influences the incidence of tumor development. Such results agree with our clinical impression that the state of thyroid function has no influence on the incidence and growth of cancers in patients. In the past twelve years we have observed various kinds of malignancy six times in 150 patients with myxedema and seven times in 1,300 patients with hyperthyroidism. In addition, 2 patients were found to have teratomas of the ovary soon after they had been operated upon for Graves' disease. The higher incidence in myxedema than in hyperthyroidism is probably related to the higher average age of patients with myxedema.

In this connection we have observed an interesting phenomenon in one of the patients with myxedema who had an epithelioma of the nose. This lesion failed to heal in spite of repeated exosures to x-ray over a period of ten years. However, as soon as the patient became normal with thyroid administration the lesion healed completely and has remained so for eight years. What the explanation for this may be is not clear. It probably has to do with the increase in blood flow in the skin, the increase in metabolism of the epithelium, and the increased rate of desquamation of epithelial cells.

There are some reports which indicate that tumor growth is retarded in thyroidectomized animals (Nishida,[6] McJunkin, Templeton, and Kravec[7]). Similar results have been recorded for hibernation and for starvation. Either depression in metabolism, common to all three conditions, or some peculiar disturbance in nutrition, present in all three conditions, may account for these results. On the other hand, Gilroy[8] reports that thyroxine injected into mice retards the rate of tumor growth, an effect which may be neutralized by the administration of arginine. A possible explanation for these confusing results may lie in the unusual findings obtained by Meyer and McTiernan.[9] These investigators found that the oxygen consumption of malignant tumor tissue from thyroidectomized animals was slightly reduced, to 15 per cent below the average, but the oxygen consumption of tumor tissue from thyroxine-treated animals was also reduced and more so, an average of 25 per cent in three-fourths of the cases. Such results indicate that malignant growths are not under the usual physiologic control.

A point of interest is the effect of malignancy on the thyroid of the host. In experimental cancer there is reduction in height of epithelium, indicating diminished function, probably preceded by a short period of stimulation (Larionow,[10] Twort and Twort,[11] and Nishida[6]). In the advanced stages of the disease there is further depression of thyroid function. In patients with any type of cancer the basal metabolism

is frequently elevated (Jura[12]), probably as a result of the toxemia produced by the cancer rather than from stimulation of the thyroid gland. As cachexia develops the metabolism remains elevated or may actually increase, but the thyroid may become atrophied as a result of malnutrition.

ENDOCRINE ACTIVITY OF THYROID TUMORS

Pathologists dealing with malignant thyroid disease disagree about the proportion of thyroid carcinomas arising from previously existing benign adenomas. Some adenocarcinomas and the various types of sarcoma do not arise from previously existing tumors. The incidence of thyroid malignancy is about 1 to 4 per cent of nontoxic goiters.

The statistics of the older literature indicate that malignancy occurred largely in goitrous areas. However, the more recent figures from various clinics throughout this country are rather uniform. For example, Means[13] reports a 3.2 per cent incidence of thyroid cancer for the nongoitrous area around Boston, and Pemberton[14] reports a 2 to 5 per cent incidence for the goitrous region around Rochester. The figures from both areas are in relation to nontoxic nodular goiter.

The question whether malignant thyroid tumors and their metastases can function normally and, indeed, overfunctionate, has led to a good deal of speculation. The classical case of von Eiselsberg[15] has frequently been cited as evidence that metastases from thyroid cancers may function normally. His patient developed myxedema following removal of the thyroid for malignancy. Two years later, myxedema disappeared when the tumor, consisting of colloid-containing follicles, recurred in the manubrium. When the tumor was removed, myxedema returned. The occurrence of tetany along with myxedema and the disappearance of tetany as the tumor recurred is further evidence that the tumor in his case was producing thyroid hormone. On the other hand, there are reports which indicate that thyroid carcinoma or its metastases do not relieve coexisting myxedema (Gulliver[16]). The fact that myxedema seldom, if ever, occurs when the thyroid is diffusely malignant does not necessarily indicate that the malignant tissue is producing hormone. It is more likely that the uninvolved normal follicles are the sites of such activity.

More direct evidence of activity of thyroid tumors has been forthcoming. Although Marine and Johnson[17] found only minute amounts of iodine in 3 thyroid carcinomas and none in the metastases, and Eisen[18] found no iodine in 1, either in the original tumor or in its metastases, other observers have reported the presence of thyroid hormone in such tumors. Graham[19] found that the iodine content of adenomas and the effect on the metamorphosis of tadpoles varied with the degree of differentiation of adenomas. One fetal adenoma and one carcinoma, each of which contained only traces of iodine, still produced a definite accel-

eration of tadpole metamorphosis. Similarly, Milles,[20] using the Gudernatsch test, and Engelstad,[21] using the Reid Hunt acetonitrile method, both showed that metastases from thyroid malignancy contained active hormone. Moreover, by means of the more recent refined methods of iodine analysis, it has been found that thyroid tumors do contain appreciable amounts of iodine. Hamilton and Soley,[22] using radioactive iodine as a tracer, determined that carcinomas of the thyroid take up 0.39 per cent radioactive iodine. The ratio of uptake was higher than normal, exceeded only by the hyperplastic glands due to iodine deficiency. Recently Keston, Ball, Frantz, and Palmer[23] reported that a femoral metastasis from a thyroid carcinoma took up 30 per cent of the radioactive iodine administered.

Another aspect of this problem centers about the question as to whether thyroid malignancy may be associated with hyperthyroidism. Means[13] states that he has not seen cancer of the thyroid in persons who have had toxic goiter. Similarly, Crile[24] did not find a single incidence of indisputable hyperthyroidism in 249 cases of thyroid malignancy, and came to the conclusion that the diagnosis of malignancy should be made with caution where evidence of hyperthyroidism is clear-cut. This would mean either that hyperplastic tissue cannot become malignant or that thyroid carcinoma cannot hyperfunctionate. Other investigators report different results. Clute[25] could find no case of cancer arising in a typical hyperplastic gland but did find 4 cases in which carcinoma developed in fetal adenoma associated with exophthalmic goiter. Coller[26] found only 1 case of thyroid carcinoma arising from a hyperplastic gland, and Pemberton,[14] studying the largest single group of thyroid tumors (774), found 10 patients with hyperthyroidism. In 4 the neoplasm was confined to adenoma in the gland; in 6 it developed within the gland. Goetsch[27] reported 7 instances in 52 cases of thyroid malignancy where the malignancy occurred in hyperplastic glands. He came to the conclusion that these tumors arose from preexisting fetal rests or nodules and not from hyperplastic cells. The highest incidence of hyperthyroidism in thyroid malignancy has been reported by Welti and Huguenin[28] (8 in 88 cases of thyroid neoplasm), and by Friedell[29] (57 in 412 cases of adenocarcinoma). Part of the variation in reported results may be due to the fact that thyroid carcinoma is frequently associated with an elevated metabolism. But this also is true for nonthyroid carcinomas. The elevation of metabolism is not necessarily due to overfunction of the thyroid but rather to absorption of toxic products from the tumor and from structures destroyed by the tumor. Moreover, a false elevation in metabolism may be obtained, especially in patients with thyroid cancer, as a result of dyspnea and stridor which the thyroid mass may produce.

My own experience corresponds to that of Means and of Crile, with one exception. Recently I was invited by Dr. F. Reichenbach of the Westfield State Sanatorium to see a patient with toxic goiter and

widespread metastases from the thyroid. She was clinically hyperthyroid and had a basal metabolic rate of plus 87 which improved on iodine. A nodule had been present in her neck for many years but had caused no symptoms. Biopsies from the nodule in the neck and from one of the metastases revealed the histologic picture of normal thyroid tissue—an example of "benign metastasizing adenoma."

I have also had the opportunity of studying the case history of another patient with hyperthyroidism and malignancy of the thyroid.* This patient was suffering from hyperthyroidism in association with acromegaly, and required subtotal thyroidectomy in 1923. She remained symptom-free until 1932, although the picture of acromegaly progressed, when the goiter recurred as well as symptoms of hyperthyroidism. In 1933, the toxic symptoms became so severe as to necessitate a second thyroidectomy. At this time a nodular goiter which was grossly and microscopically malignant was found. Following heavy radiation the patient has been free from thyroid disease until the time of this communication.

In the first case it seems clear that a pre-existing adenoma was the cause of the thyroid malignancy. However, it was not possible to determine the source of hyperthyroidism. It was my opinion that the adenoma and metastases were not producing an excess of thyroid hormone, but that the remainder of the thyroid was hyperplastic and responsible for the thyrotoxicosis. In the second case it seems likely that the recurrence of hyperthyroidism did not result from malignant thyroid tissue but rather from regrowth of hyperplastic tissue due to pituitary stimulation. It is impossible to draw any conclusions as to the origin of the malignancy, whether from hyperplastic tissue or from a pre-existing adenoma.

A case report submitted to Dr. James H. Means by Dr. H. R. Peters of Baltimore suggests that aberrant thyroid tumor tissue, in this case in the ovary, is able to produce hyperthyroidism. Similar case reports have appeared in the literature.

Briefly, this patient, a woman, 41 years of age, suffered from hyperthyroidism of moderate severity for six months. Her basal metabolic rate level of plus 34 per cent did not change with iodine medication, and thyroidectomy was carried out. The tissue removed at operation showed hyperplasia and involution. In spite of an adequate operation she continued to suffer from symptoms of thyroid intoxication and the basal metabolic rate remained at plus 30. Five months after thyroidectomy a mass was discovered in the pelvis and removed surgically. Following the second operation the patient had a thyroid storm but recovered completely. Her metabolism dropped to minus 6 and she became free from thyrotoxic symptoms. Interestingly enough, the cyst removed turned out to be a teratoma, containing hyperplastic thyroid tissue which was partly involuted.

The most important aspect, clinically, of the problem of function of thyroid tumors revolves around the disease "toxic adenoma." In

*I am indebted to Dr. John C. Roe of Pittsfield for permission to mention this case.

any large group of patients with thyroid disease one finds a few showing mild hyperthyroidism, asymmetrical goiter, and little in the way of eye signs. At operation the surgeon may find, in a case of this type, a single nodule and normal-looking or slightly atrophic tissue surrounding it and also in the opposite lobe. Should the pathologist call this nodule an adenoma then one must hold with Plummer and call this a case of "toxic adenoma"—a truly hyperfunctionating neoplasm. However, many pathologists refuse to call this nodule anything but a discrete lump of hyperplastic tissue. In that event one cannot label this case as anything but a variant of ordinary thyrotoxicosis. It is my opinion that the argument for "toxic adenoma" is inadequate. I have seen several patients whose clinical picture was characteristic of Graves' disease—with moderate toxicity, eye signs present, and response to iodine. At operation only single nodules were found that appeared histologically like the diffuse hyperplasia of ordinary exophthalmic goiter. The remainder of the tissue was normal grossly and microscopically. Perhaps this problem cannot be settled until the pathologist is able to differentiate hyperplasia from neoplasia.

CONCLUSION

1. The state of thyroid function does not seem to influence greatly the development and growth of either experimental or human cancers. The slight retardation in tumor growth produced by thyroidectomy is probably due to associated nutritional disturbances. Thyroxine, under some conditions, may also depress tumor growth.

2. Malignant thyroid tumors and their metastases probably contain small amounts of thyroid hormone, the concentration depending on the degree of differentiation. The absence of myxedema in association with thyroid malignancy is not necessarily due to the production of hormone by malignant tissue but may be due to the function of uninvolved normal thyroid tissue.

3. The association of hyperthyroidism and thyroid cancer is rare. There is no evidence that thyroid malignancy can produce an excess of thyroid hormone or that hyperplastic tissue can become malignant. It is more likely that malignancy arises in a pre-existing adenoma imbedded in the hyperplastic gland.

4. Struma ovarii may produce clinical hyperthyroidism.

5. So-called "toxic adenoma" may not be a neoplasm at all, but rather the end result of a single focus of ordinary hyperplasia.

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THE ENDOCRINE ASPECT OF ENLARGEMENTS OF THE PARATHYROID GLANDS

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DISEASE associated with tumor or hyperplasia of the parathyroid glands has been considered rare. This is because the glands defy detection and because the misconception is held that bone disease is a requisite of parathyroid disease. Parathyroid disease frequently exists; it is merely not diagnosed and not proved.

Although the parathyroid glands were described as anatomic structures as long ago as 1880, by Sandstrom,[1] pathologists were unable to contribute much to the description of parathyroid diseases; the parathyroid glands are small, of a color hard to differentiate, in position various, and they are, therefore, found only after painstaking search even at an autopsy. Parathyroid adenomas were found post mortem (Askanazy, 1904)[2] in certain cases of a bone disease with tumors, cysts, and generalized decalcification (osteitis fibrosa cystica generalisata or von Recklinghausen's disease, 1891).[3] But it was wrongly construed that the parathyroid enlargement was secondary to the bone abnormalities. It was not until 1925 that Mandl,[4] a surgeon in Vienna, tested the concept that the parathyroid tumor was the cause of the bone changes. After excising a parathyroid tumor from a patient with von Recklinghausen's disease, calcium was again deposited in the bones and hyperparathyroidism was established as an entity.

It was correctly assumed after 1925 that the clinically important primary disease of the parathyroid glands was the endocrine one associated with hyperfunction, that is, excessive production of hormone. Reports of some eighty-five cases of generalized osteitis fibrosa cystica associated with a parathyroid tumor had appeared in the literature by 1932. In contrast, first, only two cases of primary or idiopathic hypoparathyroidism[5] had been reported. Second, a few cases of a malignant tumor of the neck, supposedly in a parathyroid gland, were described; histologically difficult to prove, certainly some of the cases were doubtful. And finally, no case of a nonmalignant tumor of a parathyroid gland not associated with hyperfunction had been reported.

As a result of Mandl's discovery and various experimental pathologic observations, the idea became firmly established that the parathyroid hormone acts directly on bone and that any functional disturbance of the parathyroid glands must of necessity result in bone changes. Al-

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though historically understandable it is unfortunate that such a concept arose, for until physicians learn the correct relation of the bone disease to the parathyroid glands, only the less frequent type of hyperparathyroidism will be recognized.

As the result of the early experience with patients with von Recklinghausen's disease at the Massachusetts General Hospital it was felt probable that the primary point of action of the parathyroid hormone was not in the bones, and indeed it has developed that the majority of patients with hyperparathyroidism seen at this hospital have shown no bone changes. Since hyperparathyroidism is an endocrine disease it is fitting that credit be given the endocrinologist and not the pathologist for the recognition of its widespread nature. By his physiologic or functional approach the endocrinologist has recognized disease of the parathyroid glands and demanded that the surgeon find the pathologic gland even though minute.

CLINICAL INCIDENCE OF DISEASES OF THE PARATHYROID GLANDS

Primary Hyperparathyroidism.—Primary hyperparathyroidism per se causes no specific symptoms. The elevated blood serum calcium level, which results from excess of the parathyroid hormone, is associated with diminished muscular tone. Clinically this is registered in relaxation, lassitude, and fatigue; these are not symptoms characteristic of any one disease. The lowered blood serum phosphate level, the second classic blood finding, causes no recognizable symptoms. The third important abnormality of metabolism, increased excretion of calcium, produces but occasional polyuria and polydipsia. The disease is clinically recognizable, except in rare instances, therefore, only through its complications.

The commonest complication of hyperparathyroidism is precipitation of calcium in the urinary tract. The other major complication, but the less common one, is decalcification of the bones. This latter complication may take either of two forms, generalized osteitis fibrosa cystica or diffuse osteoporosis. From 1932 to June, 1944, there have been seventy-eight proved cases of primary hyperparathyroidism at the Massachusetts General Hospital. The complication encountered in each of the seventy-eight cases is given in Table I.

The figures in Table I give a false impression of the importance of bone disease in hyperparathyroidism. In Table II the cases are rearranged according to whether the diagnosis was first suspected at the Massachusetts General Hospital or whether the patients were referred from another clinic to this hospital for treatment with the presumptive diagnosis already made.

Three things are suggested by Table II. First, that the renal complications of hyperparathyroidism are more common than those of the bones. This is the more obvious when it is realized that more than one-

TABLE I

CLINICAL TYPES OF HYPERPARATHYROIDISM OF MASSACHUSETTS GENERAL HOSPITAL SERIES OF CASES

COMPLICATION	NO.	PER CENT
Bone Disease		
Classic	23	30
Decalcification	1	1
Decalcification and renal stones	11	14
No Bone Disease		
Renal stones	43	55
Total cases	78	

TABLE II

DIVISION OF MASSACHUSETTS GENERAL HOSPITAL SERIES OF CASES OF HYPERTHYROIDISM—WHERE DIAGNOSED

COMPLICATION	NO.	PER CENT
Massachusetts General Hospital		
Classic bone	7	11
Decalcification	0	
Decalcification and renal stones	8	18
Renal alone	36	71
Total cases	51	
Elsewhere		
Classic bone	16	59
Decalcification	1	4
Decalcification and renal stones	3	11
Renal alone	7	26
Total cases	27	

half of the patients listed in Tables I and II under bone disease also had renal complications. It is therefore clear that if one wants to find cases with hyperparathyroidism, one must look for them first among patients with renal tract calcification. Second, that the only type of the disease being diagnosed with any regularity elsewhere is the bone disease type. Indeed, three of the seven patients in which the condition was diagnosed by the renal stone and who were referred to us, came from clinics in or near Boston intimately associated with the staff of this hospital. And third, that the large number of patients treated at this hospital is not merely the result of cases being referred to us from all over the country.*

*Wilder and Howell[6] have sought an explanation for the number of cases of hyperparathyroidism reported from England and New England as compared with those found in our Central West. They suggested that the greater moisture of the seaboard air decreased the penetration of the actinic rays and increased the incidence of rickets. Rickets is known to be associated with parathyroid hyperplasia. They felt that such hyperplasia might result in tumor formation and hyperparathyroidism. If such an explanation were true a proportionate number of cases should appear in other Atlantic seaboard cities; no other clinic group has reported such numbers. The disease should be more prevalent among Negroes; this has not been reported from hospitals dealing with large numbers of Negro patients. It also involves the assumption that hyperplasia leads to neoplasia. Although there is suggestive experimental evidence for this in other gland systems it must remain an assumption. Next, the adult patients with the proved disease, here and elsewhere, both with and without bone disease, have shown no evidence by roentgenogram of previous rickets. And finally, the patients referred to us have come from states distributed over this continent.

The classic bone disease form of hyperparathyroidism is readily diagnosed; the roentgenogram is characteristic. Metabolic studies are unnecessary but, if made, the abnormalities are readily spotted even by inexperienced technicians. The patients with the renal complications and little or no bone disease, however, have generally a milder form of the disease and it is only with painstaking effort and persistent study that the disease is diagnosed.* In some of the cases of this series the diagnosis was not established until the offending gland had been excised and a change in metabolism demonstrated.

The first case studied in this country was at the Massachusetts General Hospital. Each successive case was investigated so thoroughly from the physiologic point of view that it became possible to forecast variations in the disease. It was in this manner that the primary hyperparathyroidism without the bone complications was established.

Physiology of the Parathyroid Hormone.—The end results of the action of the parathyroid hormone are well known. How the hormone effects these results remains a matter of conjecture.

There are four salient features of the action of this hormone. It exerts a control over the distribution of both calcium and inorganic phosphate ions in the blood stream and probably in all of the body fluids. Whether the hormone acts primarily on the phosphate or the calcium ion is not clear; the majority opinion favors the calcium ion. With increased activity, the level of the calcium ion in the blood serum is raised and that of the phosphate ion depressed. There is an increased outflow of both calcium and phosphate through the kidney while there is sometimes a slightly diminished fecal calcium excretion. In hypoparathyroidism the reverse of these effects is true.

The primary site of action of the hormone is not clear. It has been suggested that it is in either the kidney or the bone. The best evidence against an action in the bone, at least as far as decalcifying the bone is concerned, is the clinical finding that hyperparathyroidism exists without demonstrable changes in the bones, either microscopically or by roentgen ray, and that the phosphatase level of the blood serum is more often normal than elevated. It is possible that the hormone affects cells and that its influence on ion distribution in the body fluids is secondary.

The reason certain cases of hyperparathyroidism develop decalcification is due to the hormone's action in increasing excretion of calcium. If the intestinal tract is absorbing sufficient calcium, that is, if there is sufficient calcium in the diet, the excess excreted comes from that absorbed and the patient does not develop bone disease. If the diet is low in calcium, the excretion is at the expense of the bones, which are the storehouse for calcium. When the reserve calcium in the trabeculae of the bone is gone, the calcium is taken from the cortex.

*The number of cases diagnosed at this hospital is due to the enthusiasm and vigilance of Dr. Fuller Albright.

It is not understood why certain of those patients whose bone reserves are called upon to feed the disease process develop the complicated, distorted picture of osteitis fibrosa cystica instead of simple decalcification or osteoporosis. Possibly a greater rapidity of removal of calcium with overactivity of foreign body giant cells has something to do with the giant tumor formation so characteristic of this specialized form. It is also possible that conditions affecting the regeneration of the bone matrix, such as the lack of sex hormone after the menopause, swing the balance in favor of osteoporosis.

Since kidney stones may be a complication of hyperparathyroidism, it is imperative for physicians to understand the disordered physiology of the disease in order to differentiate stones due to hyperparathyroidism from those due to other causes. As has already been suggested, the elevation of the calcium ion causes decrease in muscular tone. (This is, of course, the reverse of the tetany occurring with hypoparathyroidism and decreased calcium ion in the body fluids.) This decrease in tone is associated with a lack of vigor and lassitude and often not appreciated by the patient until the offending gland has been excised and well-being returns. There may be mild, bizarre gastrointestinal complaints, perhaps with constipation. But usually the patient feels perfectly well and may be surprised at attention to anything but the presenting renal stone. Fatigue exists with greater elevations of the blood calcium. The polyuria and polydipsia are unpredictable symptoms; the physiologic basis presumably is the same controlling that in diabetes mellitus except in those patients who have developed impairment in renal function.

The commonest renal symptoms of the disease come from calculi. The increased output of calcium by the kidney results in supersaturation of the urine. The calcium precipitates out usually as a phosphate salt since the phosphate ion is always in excess; this is particularly true if the urine is alkaline when the phosphates are most insoluble. On the other hand, if oxalate is present, calcium oxalate may be formed. This is more likely when the urine is acid and the oxalate the more insoluble. Stones, therefore, may contain one or other salt, or mixtures, but always calcium. The precipitation may occur anywhere in the urinary tract. If it occurs in kidney substance along the tubules, gradual impairment in renal function occurs. If it takes place in the lumen of the tubules, calcium phosphate casts result. The finding of such granular casts in the urine is presumptive evidence of hyperparathyroidism.[7]

If the precipitate starts in a calyx or pelvis of the kidney, stone formation results. The symptoms are those of any stone in this position; the stones frequently become dislodged and pass into the ureter with serious consequences. Primary bladder and prostatic stones have been observed in our cases. Presumably these were due to the presence of urea-splitting organisms. The ammonia formed by the bacteria alkalizes the urine at this level and causes precipitation of calcium phosphate.

The phosphate stones are the more frequent and are of all sizes and shapes. The oxalate stones cast a characteristic snowflake shadow on the roentgenogram.

It cannot be overstressed that a mild degree of hyperparathyroidism may result in sufficient stone formation or calcification of the kidney to kill the patient. The prompt recognition of hyperparathyroidism in a patient with renal stone formation, therefore, may be lifesaving even though the hyperparathyroidism itself is so mild as to give no symptoms. Premature operation upon the kidney stone with resultant infection and alkalization of the urine may result only in increased renal tract calcification and damage. The primary operation should be on the parathyroid glands unless an emergency exists in the urinary tract.

The incidence of hyperparathyroidism in patients with renal stone is not known. Albright and I are separately agreed that this hormone disease accounts for between 10 and 15 per cent of the stone cases we see, although the figures of our general hospital are lower. This is because hyperparathyroidism is not properly excluded in all cases, and because some are so mild and have no recurrent stone formation that operation upon the parathyroids has not seemed justified.

The development of renal impairment alters the characteristics of the disordered metabolism. With progressive renal calcification or nephritis from ascending sepsis, the kidney fails to excrete the excess calcium with which it is burdened by the overactive parathyroid glands. The excess, however, is excreted by the large bowel, and the calcium level of the blood remains as before. If renal impairment continues there may be less calcium than normal in the urine.

With impairment, the kidney also fails to excrete phosphate, chloride, and nonprotein nitrogen. The levels of these three substances rise in the blood. The phosphate may rise from its abnormal, low level to normal or even above. When it is above normal it may tend to depress the elevated calcium. When retention of these substances occurs, the urine has a fixed low specific gravity, usually without albumin. The kidney function, as judged by phenolsulfonephthalein excretion, may be but little depressed.

Diagnostic Hints.—In any patient with a renal tract stone, exclude hyperparathyroidism. One or two normal blood calcium determinations are not sufficient. The disease may be in remission so the study should be spaced over a long period. A blood serum protein is taken with the calcium for if the protein is low, the protein-bound (non-ionized) fraction will be less. In this case a normal total calcium level represents an increased ionized calcium; this would be consistent with hyperparathyroidism.

In the mild cases where the blood calcium level is borderline, the phosphate level is more help than the calcium. A persistent, low, fasting

phosphate level, even in the presence of a normal blood calcium level, is diagnostic provided there is an increased excretion of calcium in the urine.

Measure the excretion of calcium in the urine, preferably in twenty-four-hour periods, using the buffer oxalate mixture.[8] This test is so simple and rapid that it can be done at the bedside. If the patient has been on a low calcium diet (no milk or milk products) for three days, more than a trace of calcium precipitate suggests hyperparathyroidism. If such calciuria persists, either hyperparathyroidism or some other cause for it must exist.

Some day hyperparathyroidism without complication of kidney or bone may be diagnosed. Such disease must exist, for in addition to the patients with renal stone and no bone disease there have also been those with the classic form of bone disease and no renal complication. These patients will suffer from fatigue and some vague abdominal discomfort.

Secondary Hyperparathyroidism.—Although hyperparathyroidism may result in impaired renal function, the reverse occurs; impaired renal function causes parathyroid hyperplasia. The current theory for this is that in patients with chronic nephritis and decreased kidney function, phosphate may not be excreted in the normal amounts and backs up in the blood and body fluids. This rise in phosphate ion concentration depresses the calcium ion to below normal levels which in turn calls forth a compensatory ovaractivity of the parathyroid glands in an attempt to maintain the calcium level at normal. This strain upon the parathyroid apparatus results in a cellular hyperplasia.

Such cellular hyperplasia is not uncommon in nephritis[9, 10] but more than a mild degree of clinical hyperparathyroidism is rarely produced. In one patient seen in this hospital,[11] the hyperparathyroidism engendered by the nephritis had developed to such an extent that the classic bone picture of von Recklinghausen's disease had been produced.

To make the differential diagnosis between primary hyperparathyroidism with extensive renal damage and secondary hyperparathyroidism due to impaired renal function may be impossible. In the latter instance the blood calcium level theoretically should never go above normal for as soon as the normal level is reached, the compensatory mechanism should cease. On the other hand, with progressive renal impairment due to primary hyperparathyroidism, the increasing phosphate retention and blood level might depress the elevated calcium level to normal or even below. Such we believe has actually been the case. And in such a patient, operative removal of the underlying parathyroid tumor (or subtotal resection of the primary hyperplastic glands) would be contraindicated.

CASE REPORT ILLUSTRATING DIFFERENTIAL DIAGNOSIS BETWEEN PRIMARY AND SECONDARY HYPERPARATHYROIDISM

CASE 68.*—A man, aged 68 years, first entered the hospital April 27, 1940, to receive roentgen-ray therapy to a basal-cell carcinoma of the scalp. The scalp lesions had been noted eleven years previously and had been treated elsewhere by excisions with grafting, and radium. He had additional complaints; for the previous one and one-half years, weakness, especially of the legs, had been progressive, and for the previous few months the patient had been bedridden. Neurologic study showed no reason for the weakness.

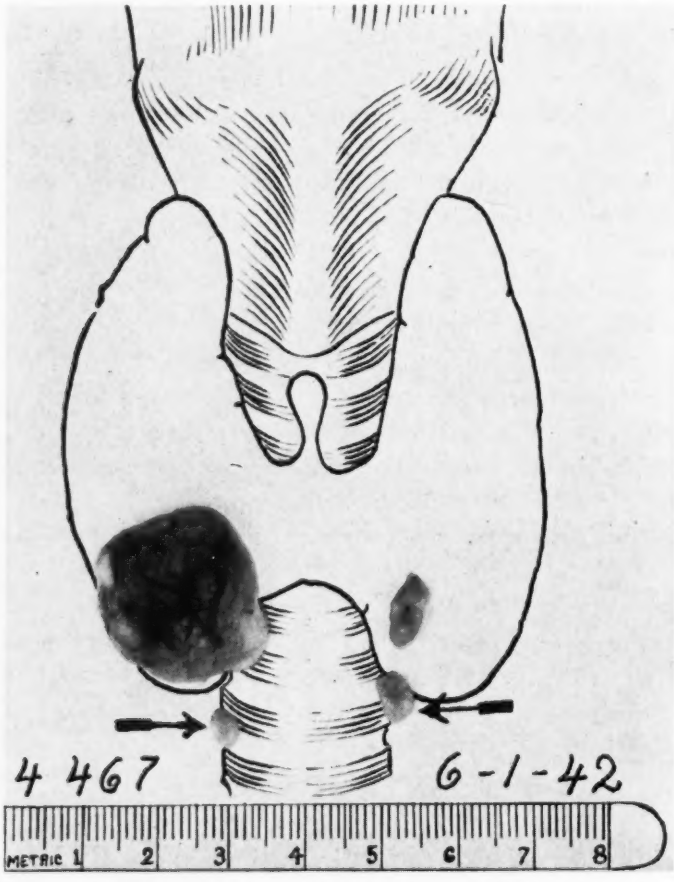

Fig. 1.—The parathyroid adenoma and the three uninvolved parathyroid glands found post mortem in Case 68. The specimens are photographed on a diagram in their relative positions to the thyroid. Arrows point to the two lower glands.

Roentgenograms.—Lateral roentgenogram of the skull showed diffuse small rarified areas; that of the chest was negative. The spine and pelvis were diffusely decalcified with a single cystlike area of destruction in the second lumbar vertebra and another in the crest of the ilium. A diagnosis of multiple myeloma was made from the roentgenograms.

Chemical studies of blood and urine failed to reveal the Bence-Jones protein or the elevated serum protein expected in multiple myeloma. The blood serum calcium

*Each case of hyperparathyroidism of the Massachusetts General Hospital series is given a number when the diagnosis is proved. The same case numbers are used in all publications on this subject from this hospital.

level was 11.2 mg. per 100 c.c., serum phosphorus 5.3 mg., and phosphatase 17.1 units (Bodansky). There was a moderate amount of calcium in the urine, a specific gravity not higher than 1.016, and intermittent albumin. Phenolsulfonephthalein excretion was only 10 to 12 per cent in two hours. A tentative diagnosis of primary hyperparathyroidism with secondary impairment of renal function was made.

Further roentgen-ray study showed decalcification of the bones of the extremities with an irregular moth-eaten appearance of some of the finger phalanges and metacarpals. A diagnosis of hyperparathyroidism was made from the roentgenograms. Additional chemical studies showed a blood serum calcium level varying between 10.0 and 11.3 mg., phosphorus 4.7 to 5.6 mg., phosphatase 19 to 22.5 units. There was a persistently high blood chloride level from 107 to 115 meq./l and low CO_2 of 16 to 24 meq./l. The serum protein was 6.4 Gm., nonprotein nitrogen 29 mg., and uric acid 6.6 mg.

A biopsy of the skull was decided upon but on the way to the operating room the patient vomited a large amount of blood and went into collapse; no bone was removed. The patient vomited blood on several other occasions. Gastrointestinal roentgen-ray studies were negative. Free acid was present in the gastric juice in normal amounts.

The medical service decided that the patient probably had primary renal disease with secondary hyperparathyroidism. The surgical service, on the other hand, judged the hyperparathyroidism to be primary, basing the decision on the slightly elevated serum calcium level (11.3 mg., the highest). Had the parathyroid overactivity been initiated by the phosphate retention, the calcium level should still have been below normal (see under Secondary Hyperparathyroidism). Operation was not advisable, however, since the renal disease had progressed to such an extent that some degree of hyperparathyroidism was thought necessary to maintain the calcium level. The elevated phosphate level would depress the calcium once any tumor was removed and the other parathyroid glands would undergo secondary hyperplasia. One form of hyperparathyroidism would be exchanged for another.

The patient was discharged and followed in the outpatient department. Sodium citrate was prescribed for the acidosis. The patient accomplished a shift in chloride and CO_2 back to normal at intervals. Clinically the patient was stronger but decalcification, as judged by roentgenograms, progressed. The blood levels of calcium, phosphorus, and phosphatase continued in the same range.

Finally, May 15, 1942, the patient re-entered the hospital with a diagnosis of pyelonephritis from which he succumbed, June 6, 1942.

At post-mortem examination, a typical, brown, encapsulated adenoma of the right upper parathyroid was found, measuring 22 by 6 mm. and weighing 2.4 Gm. (Fig. 1). The three other glands were normal in size, shape, and color. The calvarium was thin and flexible, bending like a hoop; giant cell tumors were grossly recognizable. The ilium contained a large cyst; elsewhere it and the spine were osteoporotic. The ribs were extensively decalcified and were cut with ease.

The kidney parenchyma had been severely damaged. Nowhere did the cortex measure more than 3 mm. in thickness. The corticomedullary margin could scarcely be made out and the pyramids were small and distorted. The calices of the right kidney were dilated. In the cardia of the stomach were two small leiomyomas. Microscopic sections of the lungs showed pathologic calcification.

This patient illustrates the difficulty of making the differential diagnosis between primary and secondary hyperparathyroidism in the presence of impaired renal function. He proved to have the primary form of the disease, since he had an adenoma and three uninvolved glands.

Unfortunately, making the diagnosis in this case was only of academic significance.

Benign Tumor Without Hyperfunction.—No case of a benign tumor of a parathyroid gland not associated with an excess in output of hormone has been reported. It is possible that they have been overlooked, have been thought to be thyroid, or have not been reported. That they occur is suggested by a patient operated upon in this hospital* and by the occasional finding at post mortem of small adenomas.[12] In neither of these instances, however, could pre-existing hyperparathyroidism be excluded, for the presence of a parathyroid tumor had not been suspected before either operation or death and the appropriate chemical studies had not been made.

M. G. H.* (H. No. 221018).—A woman, aged 70 years, was admitted to the hospital in October, 1939, with a diagnosis of intestinal obstruction. She had had "bilious" attacks since childhood. Five months before entry she had first noticed a lump in the left lower abdomen which had persisted. Recently she had noticed cramps radiating down the left leg associated with nausea and vomiting. There was also constipation. Abdominal examination was negative. Gastrointestinal studies were entirely negative. A nodule in one side of the thyroid was found. Roentgenogram of the chest showed old healed apical tuberculosis but no metastases. Roentgenograms of pelvis and spine were also negative for metastases.

At operation the "thyroid" lump was found to be a parathyroid adenoma measuring 6 by 3 by 3 cm. It was excised and consisted almost entirely of pale oxyphil cells; there was no evidence of malignancy.

On the fourth postoperative day a blood serum phosphorus determination was 3.8 mg. per 100 c.c. Before operation the blood nonprotein nitrogen was 2.5 mg. per 100 c.c., chloride 96 meq./l., and serum protein 7.2 Gm. No other blood studies were made. She was discharged home on the seventh postoperative day. Seven days later she suddenly died of heart failure according to her family physician.

A parathyroid tumor was not suspected preoperatively and the chemical studies necessary to exclude hyperfunction were, therefore, not made. It is probable, however, since there was no clinical tetany after removal of the tumor, that hyperfunction did not exist. This belief is strengthened by Castleman's opinion that the presence of pale oxyphil cells in large numbers in an adenoma indicate nonhyperfunction.

The tumors found at post-mortem examination by Castleman and Mallory[12] were minute, far too small to be appreciated clinically. Since all parathyroid glands are not examined at every postmortem examination at this hospital, we have no accurate idea of the incidence of such benign tumors.

Malignant Tumors.—Malignant tumors arising in parathyroid tissue have been reported but they are rare. Some twenty-two cases are reported in the literature; a good many of these are open to question since the descriptive details are meager. It is possible that the tumors

*I am indebted to Dr. Marshall K. Bartlett for permission to report this case.

in some arose from other tissue, and that others were not malignant.* There are two, recent well-reported cases in which reference to the others may be found. The tumor reported by Meyer, Rosi, and Ragins[15] from the Cook County Hospital was accompanied by undeniable hyperfunction. The malignant tumor of the other case, reported from California by Hall and Chaffin,[16] presumably did not secrete any excess of hormone.

PATHOLOGY

Enlargements of the parathyroid glands are due either to hyperplasia or neoplasia. Disordered function is associated always with the first and usually with the second. A functional or endocrine classification of the pathology of parathyroid enlargements is given in Table III.

TABLE III

FUNCTIONAL CLASSIFICATION OF PARATHYROID ENLARGEMENTS

Hyperplasia
Primary hyperplasia with hyperfunction*
Secondary hyperplasia with hyperfunction
Chronic nephritis
Vitamin D deficiency—rickets, osteomalacia
Pregnancy
Neoplasia—Benign
Adenoma without hyperfunction
Adenoma with hyperfunction
Neoplasia—Malignant
Carcinoma without hyperfunction
Carcinoma with hyperfunction

*Albright believes that hypertrophy is the proper designation for this pathologic entity.[17]

No attempt is made in this communication to give full anatomic consideration. Excellent details regarding parathyroid cell types and full discussion of the pathologic theory of neoplasia are given in the review by Castleman and Mallory.[12] The pathology of the secondary hyperplasia of the parathyroid glands in nephritis is fully described in the articles by Pappenheimer and Wilens[9] and Castleman and Mallory.[10]

Primary Hyperplasia With Hyperfunction.—Seven of the seventy-eight cases of primary hyperparathyroidism seen at the Massachusetts General Hospital have been due to a primary hyperplasia involving all four parathyroid glands. This disease type is presumably comparable to the hyperplasia encountered in thyrotoxicosis. In thyroid disease it is, however, the common type producing thyrotoxicosis, true toxic neoplasia of the thyroid being relatively rare. No clinical difference in the hyperparathyroidism produced by this pathologic type has been determined

*It may be difficult to decide whether the tumor is malignant. Dr. Broders of the Mayo Clinic and Dr. Castleman and Dr. Mallory of this hospital, for example, are not in agreement about the malignancy in the case reported by Snell.[13] After reviewing slides of the tumor, which Dr. Broders very kindly sent on, Dr. Castleman and Dr. Mallory feel it is typical of what they classify as benign neoplasia. They also have placed the case reported by Wellbrock[14] in the same category.

from that associated with neoplasia of the parathyroids. All of the characteristics of the hyperparathyroidism due to adenoma with bone and renal complications have been encountered in the seven cases due to hyperplasia. Search for other hormonal differences, such as increased pituitary hormones in the urine, have so far proved fruitless. Since this disease type is diffuse and involves all of the parathyroid tissue present, presumably the original stimulus is different from that causing neoplasia or localized disease.

The primary hyperplastic gland is grossly distinguishable from the adenoma. The surface contours are more irregular, often with deep sulci and irregular peninsulas. The color is also a deeper brown.

On microscopic section the cells are all of one type, the Wasserhelle or clear cell. There is no fat in the glands and the parathyroid cells are usually concentrically arranged with nuclei near the periphery. These cells are large and distended and measurements by Albright show that individual cells are as much as sixty times larger than those of the normal gland. Mitotic figures are rare and Albright feels that these enlargements represent hypertrophy, enlargement of the individual cells, rather than hyperplasia, increase in number of cells.[17] Castleman[18] says Albright's concept may be right but the necessary meticulous and time-consuming microscopic measurements and counts have not been done.

The gross appearance of these primary hyperplastic glands is sufficiently characteristic to be recognized at operation. It is wise, however, to check the gross observation with frozen section. A pathologist, trained in this work, can readily recognize the concentric, vacuolated cell.

Secondary Hyperplasia With Hyperfunction.—The type of hyperplasia which occurs in response to increased physiologic demand is grossly and microscopically different from the primary type. In the first place the enlargement is not as great. In vitamin D deficiency (rickets in the child and osteomalacia in the adult), and in pregnancy, the hyperplasia of the epithelial elements is mild; grossly the enlargement is not more than two to four times the normal. There is no distortion of shape or pseudopod formation. Since the enlargement is not great enough to eliminate the fat cells by compression, the color remains nearly the light brown of the normal gland.* Following long-standing nephritis, this secondary hyperplasia may continue until the individual gland weighs thirtyfold the normal.

The microscope shows the hyperplastic cells to be entirely chief cells; no water-clear cells are seen.

A mild degree of secondary hyperplasia may be difficult to recognize grossly (or even microscopically on frozen section) at operation. Long training at the post-mortem table is necessary.

*The color of the normal parathyroid gland depends upon the proportion of epithelial to fat cells contained within the gland capsule. The parathyroid epithelial cells are brown. The fewer the fat cells, therefore, the browner the gland.

Adenoma Without Hyperfunction.—The adenoma without hyperfunction differs in no way grossly from that forming an excessive secretion. The one large and few small adenomas of this type which have been encountered in this hospital have shown nonvacuolated epithelial cells, usually of the pale oxyphil type; no fat was present between the epithelial cords. The large adenoma removed by Bartlett at operation weighed 23 Gm. The small ones recovered at the post-mortem table have been scarcely large enough to be recognized grossly.

Adenoma With Hyperfunction.—Benign neoplasia or adenoma is the common pathologic type encountered in primary hyperparathyroidism. Seventy-one of the seventy-eight proved cases at the Massachusetts General Hospital were of this type. Usually the adenoma is single, involving only one of the four parathyroid glands. Five of the seventy-one patients, however, have proved to have two adenomas, one in each of two glands. The adenomas vary considerably in size; several of them have been very small, two of them were not more than 2 mm. in diameter and occupied only part of the space within the gland capsule, the remainder of the tissue being normal. In such cases the adenoma may be hard to recognize, for the presenting surface of the gland may be normal tissue.

It is not until the gland is turned over or cut into that the darker brown of the adenoma without fat cells is recognized. With increase in size, the normal tissue is apparently destroyed by compression within the capsule. With their browner color, the larger adenomas are readily recognized. The surface is generally smooth and pseudopods are rare. The color varies from light, to dark, to greenish brown. Sometimes there are small cysts within them. The largest tumor in this series weighed 53 Gm. (Larger tumors have been reported.[13]) The size of the adenoma is roughly proportional to the elevation of the blood calcium above normal.

Microscopically, adenomas have been found to contain all of the various cell types. Some are composed of one type alone and others of mixtures. Fat cells in the stroma are rare.

Carcinoma.—No case of carcinoma of the parathyroid gland has been recognized at this hospital. That such malignant tumors do occur has already been alluded to and reference should be made to the reports of Meyer, Rosi, and Ragins[15] and Hall and Chaffin.[16] It is probable that such malignant tumors are rare since it is difficult to imagine that a cancer would be overlooked even in a routine post-mortem examination where no effort is made to identify the parathyroid glands.

It is possible that the relative incidence of malignant to nonmalignant neoplasia is the same in both the parathyroid and thyroid glands. Carcinoma of the thyroid is not infrequent but abnormalities of the thyroid gland are probably far more numerous than those of the parathyroid. It has been denied that carcinoma of the thyroid can be associated

with hypersecretion. Certainly in the case of the parathyroid, carcinomatous tissue can secrete an excess of hormone.

Atrophy.—Primary atrophy with hypoparathyroidism is a clinical curiosity, but secondary atrophy of the uninvolved glands in the presence of a hyperfunctioning adenoma is common and of direct clinical and surgical importance. If an atrophic gland is uncovered at operation, the atrophy points to the presence of a hyperfunctioning adenoma in another gland. This secondary atrophy, or atrophy of disuse, can be recognized grossly by the surgeon.

The atrophic glands are not only smaller than the expected normal but the color is yellower since the atrophy affects the epithelial and not the fat cells. In the presence of a long-standing, active adenoma, the atrophy may proceed to such a degree that grossly the uninvolved atrophic gland resembles fat and is recognized only by its capsule and characteristically arranged blood supply. A piece of one such gland was removed for biopsy and the microscopic sections showed complete absence, or atrophy, of epithelial elements. Milder degrees of atrophy may be harder to recognize both grossly and microscopically because of the variation in fat content of the normal gland.

Bone and Kidney.—Bone and kidney are not endocrine tissue but are the structures most commonly affected in the complications of hyperparathyroidism. The reader is referred to the article by Jaffe on osteitis fibrosa cystica generalisata[19] for an account of this specialized type of bone pathology. It should be recalled, however, that diffuse osteoporosis or decalcification also follows overactivity of the parathyroid gland. No adequate description of this pathologic type has appeared; a report by Albright and co-workers[20] contains certain thoughts on this subject. The pathology of the kidney, secondary to hyperparathyroidism, is briefly described by Albright and his associates.[21]

Pathologic calcification occurs elsewhere in the body in severe cases of hyperparathyroidism. Calcification of arteries is not infrequently seen by roentgenogram. In the Massachusetts General Hospital series, calcification of the gastric mucosa was found post mortem in Case 6, and of the lung in Case 68 (see case report in this communication). Such calcification has been demonstrated in experimental animals with parathyroid poisoning.

TREATMENT

It is not the purpose of this article to deal in detail with treatment. For a complete discussion of this aspect of the parathyroid problem, reference should be made to the other articles from this hospital.

Medical therapy in the form of a high calcium diet has been suggested for hyperparathyroidism. It is true that the bones can be recalcified[21] in the presence of the active parathyroid disease but kidney damage is accelerated. With the increased intake of calcium from the intestinal

tract the bones are spared but the load of the kidney is multiplied. Rapid calcification of renal tubules and stone formation may result in progressive impairment of renal function. Stones can be removed but the impairment due to renal calcification has, in our experience, proved irreversible.

Roentgen-ray treatment in hyperparathyroidism has been ineffectual; this is discussed in detail elsewhere.[22] The use of irradiation in the treatment of carcinoma of the parathyroids has not been reported.

The treatment of parathyroid enlargements, tumor or hyperplasia, is surgical. If a tumor is not accompanied by disordered function, it should be excised with capsule intact. If the tumor is malignant, radical excision including the area of lymphatic drainage is indicated. The use of postoperative irradiation should be considered.

If hyperparathyroidism is present there are special considerations which should guide the surgeon in his attack. These have been fully described elsewhere.[23] The operation may have to be divided into two stages (10 per cent of cases). Subtotal excision of primary hyperplastic glands is always indicated, and of an adenoma, in the presence of extensive bone disease, sometimes.

SUMMARY

Enlargements of the parathyroid glands are not uncommon. Those associated with hyperfunction are clinically the most important. The endocrine considerations of the hyperplasia and tumors causing primary and secondary hyperparathyroidism have been discussed. A case of hyperparathyroidism with severe renal damage is described to illustrate the difficulty in differentiating between primary and secondary hyperparathyroidism, and also to emphasize the renal complications of this disease. A functional classification of the pathology of parathyroid enlargements is given. The clinical types of hyperparathyroidism encountered in the seventy-eight cases of the Massachusetts General Hospital series are given in table form. The treatment of parathyroid enlargements is surgical.

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HYPERINSULINISM IN RELATION TO PANCREATIC TUMORS

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THE endocrine function of the pancreas in carbohydrate metabolism is now well established but the story of the development of our knowledge of the internal secretion of islet cells is a long one. In 1788, Cawley[1] reported the autopsy findings of pancreatic calculi in a patient dying of diabetes mellitus. This was perhaps the first time that the pancreas was suspected of having an etiologic relationship to diabetes. Claude Bernard[2] discussed glycosuria and hyperglycemia, in 1856. In 1869, Paul Langerhans,[3] while still a medical student in Berlin, published his remarkable histologic studies of the pancreas in his inaugural dissertation. Using the transillumination method in living tissue, as did Lister[4] in his study of inflammation and recently revived by Knisely[5] in the study of the spleen, Langerhans described the several types of cells and tissues in the pancreas, and by his original method of dye injections showed the acinar gland tissue to be separate from islet tissue.

These collections of cells, which he termed "unser zellen," were given scant notice. In 1884, Arnozan and Vaillard[6] ligated the ducts of the pancreas and noted an atrophy of the acinar tissue and the persistence of islet cells, but did not attribute any significance to these cells in the fact that the animal did not develop a diabetes.

In 1890, von Mering and Minkowski[7] proved experimentally that a fatal diabetes can be produced in animals by total pancreatectomy. Two years later Minkowski[8] carried out an even more conclusive experiment. He successfully grafted pancreatic tissue subcutaneously. In the same animal the remaining pancreas was excised later without the development of glycosuria; but on removal of the graft the animal died of a rapidly developing diabetes. An endocrine function was postulated but the exact tissue involved was not proved.

In 1882, Kühne and Lea[9] described the capillary network surrounding the collections of islet cells, but did not contribute to the morphology of the cells themselves. In 1893 appeared the first report of a very real student of the endocrine function of the pancreas. In this report Laguesse[10] discussed the islet cells and generously called attention to their discoverer and named them "les ilôts de Langerhans." He de-

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scribed the histology of the cells, including the granules, and the capillary network, and suggested the possibility of an endocrine function of these cells.

In 1895, Schäfer[11] called attention to the evidence in favor of an internal secretion of the pancreas as shown by fatal diabetes with total pancreatectomy while a total external fistula resulted in no diabetes. In 1900, Ssobolew,[12] as a result of duct ligation experiments with persistent islands, predicted that the study of the chemistry of these isolated islands would place organotherapy in diabetes on a rational basis. He even advised the use of newborn animals (calves) in which the islands are well developed in comparison with the acinar tissue, and made the following prediction: "We are justified in the hope that in the near future the question will be decided whether or not this method of approach will succeed in relieving the ills of the diabetic patient."

During the next twenty years a number of investigators were very near the crucial demonstration of this internal secretion, but failed because the extract of the islet tissue was not used in sufficient amount in a totally pancreatectomized animal with diabetes, or because of impurities in the extract. It remained for Banting and Best[13] of Toronto to demonstrate to an expectant world, by positive and conclusive experimental physiology, that islet tissue has an internal secretion, since named insulin, and that it can be used successfully in the control of diabetes. Their epoch-making announcement was made in 1922.[13, 14]

During this period of 1900 to 1922 a number of contributions were made in the histologic field. Opie,[15] in 1901, described hyaline changes in the islet cells of diabetics. In 1906 and 1908, Lane,[16] by special technique, demonstrated two types of granule-containing islet cells and called them the *alpha* and *beta* cells. Bensley,[17] in 1912, described a vital staining technique for counting the islands in the guinea pig and demonstrated that islet cells are derived from duct epithelium.

Homans[18] studied experimental diabetes and, in 1915, showed changes in the *beta* cells of the islands. After the discovery of insulin Copp and Barclay,[19] repeating Homan's experiments, demonstrated that administration of insulin restored the exhausted *beta* cells.

In 1930, O'Leary,[20] using transillumination in the pancreas of the mouse fed with glucose, was able to see vacuoles form in the islet cells. These vacuoles migrated to the periphery of the cells next to the capillaries into which they apparently disappeared by diffusion.

PATHOLOGY OF ISLET TISSUE

The study of degenerative changes in the pancreas in diabetes began with Hanseman's[21] report, in 1894, on fibrosis and atrophy of the pancreas in diabetic patients. Ssobolew's[12] observations and Opie's,[15] which were made independently, have been mentioned. Homans,[18] in 1915,

described changes in experimental diabetes in the dog's pancreas confined to the *beta* cells of the islands.

It was not until the significance of the islands as insulin-producing cells was understood, and not before the syndrome of insulin shock was appreciated, that the islet-cell tumors or hyperplasias received any attention by the pathologists. In 1902, Nicholls[22] described the first of these tumors, but gave no clinical history. Ssobolew,[23] in 1904, was the first to report a hypertrophied island in the autopsy of a diabetic. Herxheimer,[24] in 1905, and MacCallum,[25] in 1907, described similar findings. In 1920, Dubreuil and Anderodias[26] made a most interesting autopsy report on the hypertrophied islands of a newborn infant of a diabetic mother.

Even as late as 1926, four years after the discovery of insulin, only sixteen islet-cell tumors had been described. In that year Warren[27] reviewed these and four of his own cases, but no physiologic significance was attached to these growths. In the same year Gray and Feemster[28] described the hypertrophied islands of an infant born of a mother with diabetes. The child died of convulsions shortly after birth. Shortly after the phenomenon of overdosage of insulin began to be observed by those who were using insulin to treat patients with diabetes, Seale Harris of Birmingham, Ala., noted very much the same syndrome in patients showing a hypoglycemia and the idea occurred to him that overactive islet tissue, either as hyperplastic or neoplastic cells, might explain the clinical picture which he had observed in these patients. Harris discussed this possibility with Banting who agreed with him in his hypothesis, and published his report[29] entitled "Hyperinsulinism and Dysinsulinism," in 1924. Three years later a physician suffering with the syndrome of severe insulin shock went to Rochester, Minn., and was studied by Wilder and his associates.[30] The patient was operated upon by W. J. Mayo, who found a tumor of the pancreas with metastases to the liver. The biopsy showed an islet-cell tumor. Several weeks later autopsy revealed the same tumor and a biologic assay of the liver metastases showed large amounts of insulin in the tumor tissue.

In 1929, Graham of Toronto removed for the first time a benign adenoma of islet tissue from a woman who had been studied by Howland and his associates.[31] The patient was immediately relieved of her symptoms and has remained well to date. This initiated a new and the latest phase of endocrine surgery, a type of surgery requiring the skill in diagnosis and operative technique previously demonstrated in the removal of tumors or hyperplasias of the thyroid, pituitary, adrenal, and parathyroid glands.

Since 1929, well over 149 islet-cell tumors have been found in patients showing hypoglycemia, some by surgeons, the rest by pathologists. Of these tumors, 106 were pronounced benign adenomas, 28 questionably malignant; in 15 cases the tumors were unquestionably malignant because of metastases to the liver or adjacent lymph nodes.

At this point it should be stated that hypoglycemia may occur without any demonstrable lesion in the pancreas, and that tumors, having all the morphologic characteristics of islet-cell growths, may be found by the surgeon or pathologist, without any of the symptoms or laboratory findings of the hypoglycemic state. Furthermore, the size of the tumor in cases of hypoglycemia does not necessarily determine the degree of insulin shock. But the carcinomas of islet tissue with metastases always show severe symptoms and very low fasting blood sugars.

Fig. 1.—Two islet-cell tumors from same patient removed at one operation.

In general these islet-cell tumors are small, averaging 1 to 2 cm. in diameter. The largest tumor, one reported by Brunschwig,[32] measured 15 by 13 by 10 cm. but did not show more severe symptoms of hypoglycemia than many other tumors of 2 cm. diameter. The largest tumor removed by the writer (3 cm. in diameter) was palpable before operation and was considered to be a tumor of the pylorus because of x-ray studies and showed no symptoms of hypoglycemia. These tumors are more frequently found in the tail or body of the pancreas where islet tissue is more abundant. But enough of these tumors are found in the head of the pancreas, in twelve cases in our series, to demand a thorough search of the head by mobilizing the duodenum so that the head can be palpated between thumb and fingers. Furthermore, more than one tumor has been found in hypoglycemic cases. For this reason a thorough search of the entire organ after the finding of one tumor should be made.

In the gross the benign tumors are encapsulated, as are many of the questionably malignant ones. These tumors are usually of a reddish to lilac color, as contrasted with the yellowish or ivory color of the surrounding pancreas, because of their rich capillary network. Many of the tumors show various types of degeneration, as hyaline and fibrous, and some are markedly calcified. In consistency they are definitely firmer than the surrounding pancreatic tissue and feel like encapsulated marbles to the palpating fingers. For this reason they have

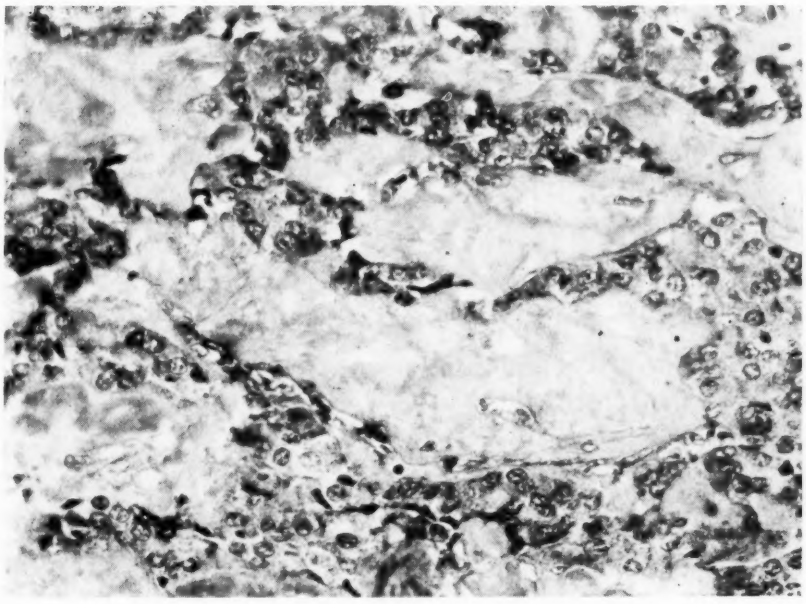

Fig. 2.—Hyaline degeneration of islet-cell tumor.

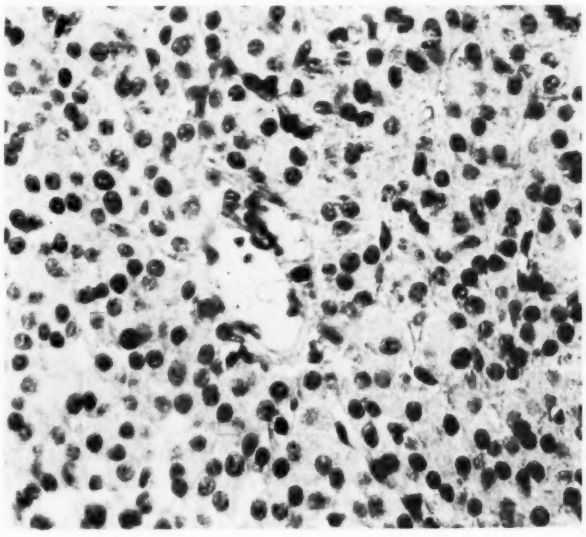

Fig. 3.—Adenomatous arrangement of islet-cell tumor.

to be palpated between thumb and fingers of the surgeon's hand if they are deeply embedded in pancreatic tissue and not visible on the anterior surface of the organ.

On microscopic examination these tumors, benign, questionably malignant, or malignant, all show cells typical of islet cells, but they

differ markedly in their arrangement and differentiation. Some are typically adenomatous, resembling hundreds of agglomerated islands; others are less well differentiated with the cells arranged in ribbons or in scattered collections of islet cells with varying amounts of degenerated fibrous tissue; still others, in the questionably malignant group, show less differentiation with some invasion of the capsule and the presence of islet cells in the capillary vessels; and lastly the definitely malignant tumors show lymph node, liver, and other metastases.

In all of these tumors the demonstration of the *alpha* and *beta* cells requires careful differential stains in freshly removed tumors and even with these stains it is difficult or impossible to demonstrate these cells.

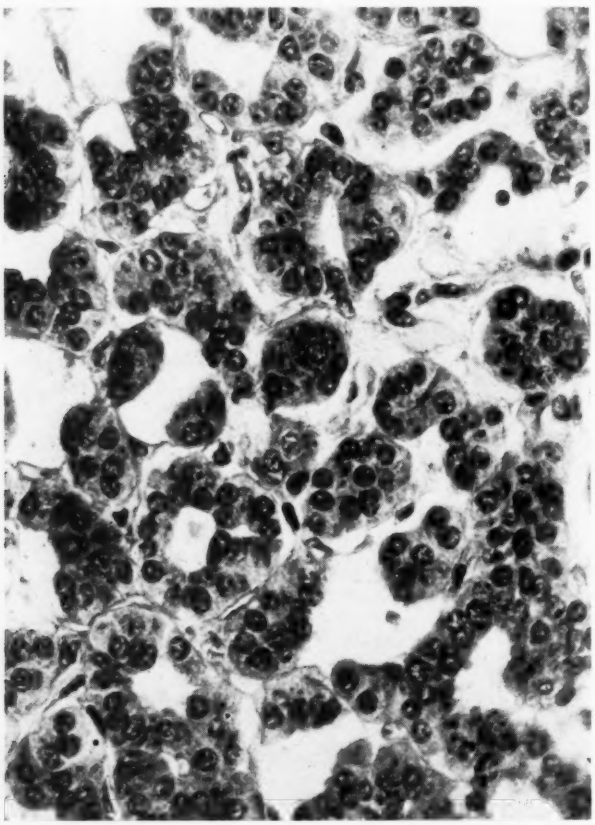

Fig. 4.—Glandular arrangement of islet-cell tumor.

The most difficult group of these tumors for the pathologist to interpret and to prognosticate are the so-called questionably malignant growths. Frantz,[33] of our surgical department, has made a special study of these tumors and has published her report on our cases. I quote from her last two paragraphs:

> It seems improbable that all of the tumors with histologic suggestion of carcinoma were really such, as the proportion of these to the benign tumors is so high, 21 to 70, and the follow-up in some cases is so long.

It would be gratifying to feel that surgery had eliminated malignant disease in all these cases. But, of these suspected tumors, are there some in which blood vessel invasion, demonstrated, means that metastases, not demonstrable, were present at the time of removal of the primary growth, and will these eventually develop symptoms of hyperinsulinism?

If one wishes to consider the so-called "adenoma malignum" type of carcinoma of the thyroid as possibly analogous to these well-differentiated islet cell tumors with blood vessel invasion, then it might be that, like the thyroid tumors of this type, distant metastases might be late and slow. But the metastasizing tumors of the thyroid do not give evidence of their presence by hyperthyroidism, and it is conceivable that even in small metastatic foci of islet cell tumors hypoglycemia might occur early. Thus far no reported case has illustrated this, but it seems a good possibility. How long one should wait to feel secure about such functional metastases, and whether one can predicate that symptoms should appear early, is pure speculation. It will be of the utmost importance to follow all of these patients with these rare tumors for many years, and in the event of recurrence, or metastases after apparently successful removal, to publish such findings so that clinician and pathologist will have some basis for prognosis.

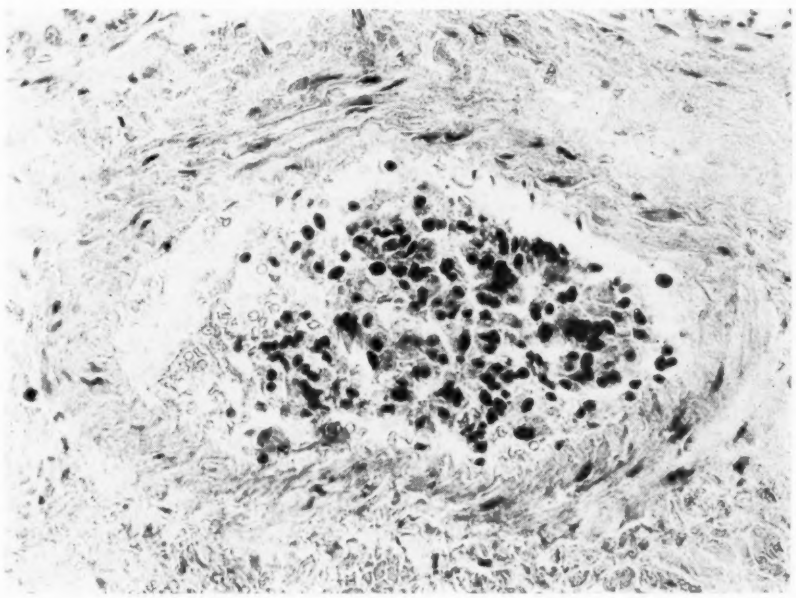

Fig. 5.—Islet cells in blood vessels of a questionably malignant islet-cell tumor.

We now have 8 of these cases, with death in 1 and follow-up studies in 7 of them, the postoperative interval being 72, 48, 24, 14, 12, 8, and 4 months. None of these patients has as yet shown evidences of recurrent hypoglycemic symptoms, which one would expect with even small recurrent growths of this type of endocrine tumors.

More recently Duff[34] has published a comprehensive review of this subject and records 12 cases of islet-cell carcinoma with tumor metastases. The reader interested in a more detailed discussion of the gross

and microscopic findings in islet-cell tumors in general is referred to the reports of Whipple and Frantz,[35] Frantz,[33] O'Leary and Womack,[36] Laidlaw,[37] and the most recent article by Duff.[34]

THE ORIGIN OF ISLET-CELL TUMORS

The genesis of these tumors has been studied by Bensley[38] and Grauer[39] on the basis of the embryology and regenerative process in the pancreas. They have demonstrated that the epithelial cells of the islands in the embryo differentiate from the epithelial cells of the small ducts of the pancreas. This ability of duct epithelium to differentiate either into islet tissue or normal ducts is seen in the adult pancreas that is regenerating after the release of experimental duct ligation. This may explain the occasional finding of an islet-cell tumor without evidences of hyperinsulinism. That is, such a tumor may not have taken on the physiology of islet tissue, although having the morphology of islet tissue.

FACTORS IN BLOOD SUGAR MAINTENANCE

A very confusing factor in many individuals with the syndrome of hypoglycemia is the question of whether or not hyperinsulinism is the cause of the hypoglycemia. The latter can be measured by blood sugar determinations, but the former is not as yet measurable. But hypoglycemia is not always the result of an overproduction of insulin. The maintenance of the normal blood sugar level is the result of an interplay of several organs, especially the pancreas, the liver, the hypophysis, the adrenals, and the thyroid. Carbohydrate ingestion in the normal individual, or the withholding of it, does not play as important a part in the maintenance of normal blood sugar level as one would suppose. It is certain lesions in the previously mentioned organs that cause a hypoglycemia. Regarding the liver, Mann[40] in his experiments with complete and partial removal of that organ has proved the essential role of the liver in this respect. Bodansky,[41] Underhill,[42] and Sprague[43] have demonstrated the effects of liver damage in the maintenance of normal blood sugar.

Of equal significance is the work that has been done in showing the role of the anterior lobe of the hypophysis in the maintenance of the blood sugar, especially that of the Argentinian Houssay.[44] Hypophysectomy causes a marked fall in the fasting blood sugar, as well as a marked sensitivity to insulin injection. In a totally depancreatized animal with diabetes, removal of the anterior lobe of the hypophysis will prolong the life of the animal and even glycosuria may disappear. Young[45] has been able to produce experimentally a permanent diabetes in dogs by the injection of an extract of anterior pituitary lobe, but he considers this a somewhat different type of diabetes from the pancreatic variety.

That there may be an intermediary action by the adrenal cortex on the anterior lobe of the hypophysis in its influence on carbohydrate metabolism is strongly suggested by the studies of Long and Lukens.[46] Womack[47] suggests that the action of the sympathetic system and the thyroid gland in the maintenance of blood sugar levels is similar to that of the adrenal medulla in mobilizing sugar from the liver.

It is obvious that the hypoglycemic state requires a careful search for the cause of the low blood sugar and that hyperinsulinism must not be assumed to be the cause until lesions or disturbances in the liver, the pituitary, the adrenals, and the thyroid have been ruled out. In liver lesions causing hypoglycemia the patients are gravely ill and show other obvious signs of liver damage. Similarly the cases due to adrenal disease are not easily confused with hyperinsulinism, for the patients are usually seriously ill with Addison's disease or show signs of adrenal tumor. The low blood sugar levels associated with hypophyseal lesions are likely to cause more confusion, but they are usually associated with tumors causing headache and with visual field disturbances, and show x-ray evidence of widening or destruction of the sella turcica. In cases of hypoglycemia with hyperthyroidism the basal metabolism rate is apt to be lower than in other cases of Graves' disease and these patients may develop a thyroid storm after the removal of an islet-cell tumor. For this reason a basal metabolic determination should be done in all cases of suspected islet-cell tumor, and if the rate is above 15 the patient should be given a course of iodine therapy as in preparation for a thyroid operation.

Finally, cases of epilepsy may mimic the syndrome of hyperinsulinism, because of the occurrence of "fits" or "spells." Electroencephalograms have proved of the greatest help in differentiating the epileptiform attacks from those seen in hyperinsulinism.

THE SYNDROME OF HYPERINSULINISM DUE TO ISLET-CELL TUMOR

Hypoglycemia due to hyperinsulinism may be the result of overproduction of insulin by overactive normal islands, by hyperplastic islands, or by tumors of islet cells, or it may be due to an overdose of insulin. The syndrome of hyperinsulinism is as varied in its manifestations as is insulin shock, for they are the same.

The "attacks," "fits," or "spells," as they are spoken of by the patient or his family, are extremely variable in their manifestations in different individuals but as a rule maintain the same general pattern, varying in severity, in the same individual. Wilder[48] has wisely grouped the nervous manifestations of these attacks under three main headings: Those relating to disturbances of the vegetative nervous system, appearing as nausea, sweating, pallor, flushing, chilliness, syncope; those related to the central nervous system, manifested by restlessness, tonic or clonic muscle spasms, opisthotonos, convulsions; and lastly those

manifestations less readily localizable under the heading of psychic disturbances such as apprehensiveness, confusion, disorientation, mania, unconsciousness, and coma.

Less frequently associated with these "attacks" are digestive disturbances and abdominal pain, at times so severe as to be mistaken for lesions requiring surgery. Harris[49] and Bickel[50] have called attention to these gastrointestinal manifestations:

1. The "attacks" come on characteristically in the early morning during the fasting period before breakfast or after severe mental or physical effort when the sugar reserves are low

2. During the "attacks" or "spells' or after a fast of twelve to twenty-four hours the blood sugar levels are always below 50 mg. per cent; and finally

3. The victims of these spells are brought back to a normal state, that is, recover from whatever their "pattern" may be, on the administration of sugar by mouth or by vein.

This essential triad which we first emphasized in our report published in 1938[51] has been corroborated in practically all of the subsequent cases and the triad has come to be considered as a sine qua non for the diagnosis of hyperinsulinism due to an islet-cell tumor. Because we have adhered to this rigid criterion we have found a tumor in 27 of the 32 patients upon whom we have operated for the hypoglycemic state. This is a much higher percentage of positive findings than that reported from any other series of operations. In only 1 of the 5 patients we explored without the finding of a tumor was the triad typical. In the other 4 we had made reservations regarding the diagnosis and were doubtful of the presence of a tumor.

THE DIFFERENTIAL DIAGNOSIS OF ISLET-CELL TUMOR WITH HYPOGLYCEMIA REQUIRING SURGERY

In many cases of hypoglycemia surgical therapy is either not required because the symptoms are controlled by conservative measures or is contraindicated because the hypoglycemia is due to causes other than islet-cell tumor. These have been discussed under the last heading.

In the study of these cases in which tumor was suspected the establishment of the triad depends upon certain laboratory studies, the most important being at least three fasting blood sugar determinations, for it will be found that these levels will vary. If after twelve hours the blood sugar is not below 50, a longer fast should be given, under supervision, to make sure the patient is not taking any food. These fasting blood sugar determinations are by far the most important of the laboratory studies. The glucose tolerance test is only misleading in its information. It is more of a liver function test and should be reserved for the period during which the electroencephalogram pattern is being studied.

THE SURGICAL THERAPY FOR ISLET-CELL TUMOR

For the patient exhibiting the typical triad and in whom hepatic, pituitary, adrenal, thyroid disease and epilepsy have been ruled out, surgery is definitely indicated. The three chief reasons for not continuing conservative therapy are:

1. Continuous administering of sugar and carbohydrate to control, but not cure, recurring insulin shock in these cases usually results in great obesity and when finally surgery is advised as a last resort, the patients have become a bad risk and a very difficult technical problem for the surgeon. Twenty-four of the 32 patients reported from this clinic were obese at the time of operation and several of them excessively so, one weighing 235, one 240, and one 278 pounds (Fig. 6).

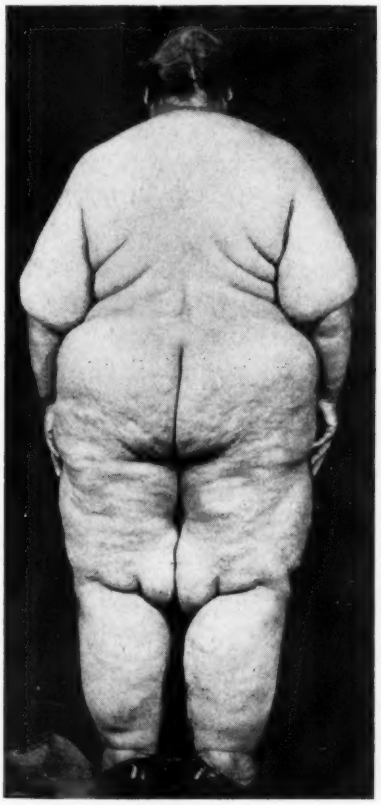

Fig. 6.—A problem in surgery as a result of obesity.

2. Prolonged hypoglycemia has a tendency to cause mental deterioration, probably due to malnutrition of the cortical cells. Two of our patients with tumors had been in mental institutions, and one of them has had to be readmitted to a mental hospital several times, having returned there at the time of this communication, although the hypoglycemia has been cured. Three others are mildly peculiar.

3. The uncertainty of when a benign islet cell tumor may show malignant changes is a definite reason for not postponing surgery in a patient with a definite diagnosis of islet-cell tumor.

The confidence of the well-trained surgeon to explore and to resect the pancreas has increased amazingly in the past ten years, for in this time astonishing advances have been made in the surgery of pancreatic tumors. Adequate incisions, better anesthesia, and the use of fine silk, with the more delicate handling of tissues and the reduced trauma and better hemostasis that "silk technique" connotes, as well as present-day methods of preventing and combating shock, are the chief factors in broadening the field of pancreatic surgery.

As a result of experience in islet-tissue tumors, resections of the body and tail, and pancreatico-duodenectomy for carcinoma of the ampullary and periampullary areas, we have adopted the following measures and technique for the surgery of islet tumors:

1. It is essential to give the patient an ample supply of glucose before the operation. We give 1,000 c.c. of 5 per cent glucose in normal saline solution intravenously one hour before operation and leave the needle in the vein for a transfusion, if necessary, at the end of the procedure.

2. Both continuous spinal anesthesia and ether anesthesia have been used, depending upon the individual indications. Excessive obesity is a contraindication for spinal anesthesia.

3. We are convinced that an adequate incision is essential and the long curved transverse incision just above the umbilicus through both recti, followed by the division of the gastrocolic omentum, provides a free inspection of the entire pancreas.

4. The islet tumors are most frequently found in the tail or body, and should be looked for there first. If a tumor is not seen on the anterior surface, the peritoneal attachment along the inferior border should be divided and, by blunt dissection and elevation, the posterior surface of body and tail should be inspected. If none is seen, the gland should be carefully palpated. The islet tumors feel like discrete nodules firmer than the surrounding pancreatic tissue even when imbedded in the body and head of the organ, and are unmistakable.

5. If no tumor is seen or felt in the body or tail, the duodenum should be mobilized to the midline by incision of the peritoneum along the curve of the duodenum. This gives access to the posterior surface and permits the essential and free palpation of the head of the pancreas. In 6 of our patients the tumors were situated in the posterior aspect near the ampulla of Vater and the most careful dissection was required to avoid injury of the papilla in removal of the tumor.

6. If one adenoma is found, the same careful search must be made because more than one tumor may be present. In 3 of our 27 cases more than one tumor was found.

7. In removing the adenoma bleeding, as a rule, is very easily controlled, and the nodule shells out easily. Drainage is not necessary unless there is pancreatic duct leakage.

8. If no tumor is found after the very complete exploration described, the decision as to resection will have to be made. In the cases where no tumor was found and the body and tail, that is, to the left of the superior mesenteric vessels, have been removed, the results have been much better than the removal of a small portion such as the tail. In order to carry out this radical resection, it is advisable to remove the spleen as well, in order to control hemorrhage by ligating the splenic vessels supplying the body and tail of the pancreas. A wide division of the gastrocolic and gastrosplenic omenta will facilitate this splenectomy through the lesser sac, and make it possible to remove the spleen, tail, and body of the pancreas en masse. This maneuver also makes it possible to see and identify the inferior mesenteric vein and the superior mesenteric vessels.

9. The bed of the pancreas should be drained after ligating the pancreatic duct, by rubber dam tubes or cigarette drain.

10. The use of fine silk for all smaller vessels and a heavier grade for the larger vessels will prevent the digestion of ligatures which occurs when catgut is used in pancreatic tissue. Fine interrupted silk sutures for the repair of the abdominal wall have given us primary union in all our cases of adenoma and the same invariable satisfaction in wound healing that was noted by Kocher, Halsted, and other meticulous surgeons familiar with silk technique.

In reviewing the results of surgical therapy for islet-cell tumors in this series, it is obvious that excision of adenomas and so-called questionably malignant tumors gives brilliant and lasting cures of the hypoglycemic state. On the other hand, in the majority of the patients in whom an islet-cell tumor was not discovered and a partial pancreatectomy was done results were not good, either because a tumor was overlooked in the head of the organ or because an insufficient amount of the pancreas was removed. This is demonstrated by the fact that an overlooked tumor was found at the second operation in eight patients, four of whom we had explored the first time and the other four in other clinics. The fact that seven of the overlooked tumors were in the head of the pancreas emphasizes the importance of an adequate exposure by a transverse incision with mobilization of the duodenum so that all parts of the head of the organ can be carefully palpated. The recurrence or persistence of hypoglycemia below the 50 mg. per cent level after a partial pancreatectomy is almost certain evidence of an overlooked islet-cell tumor.

The prognosis in carcinoma of islet tissue, that is with metastases, is invariably bad. Even the use of alloxan, as suggested by the work of Dunn,[52] and as tried by Brunschwig and associates[53] in a recently reported case, does not offer any result.

Four patients, although relieved of their hypoglycemia, have continued in a more or less unstable mental state and one of them has had to be committed to a mental hospital. All of these patients had had a severe hypoglycemia for from two to six years. This is a definite reason for advising surgery as soon as the diagnosis of islet-cell tumor with hypoglycemia is established.

TABLE I

SUMMARY OF STATISTICS

	SINGLE	MULTIPLE	TOTAL	% MULTIPLE
Tumors removed at operation and considered benign	65	11	76	
Tumors found at autopsy and considered benign	26	4	30	
Total benign tumors	91	15	106	14.2
Tumors removed at operation and suspected malignant	22	4	26	
Tumors found at autopsy and suspected malignant	2	0	2	
Total tumors suspected malignant	24	4	28	14.3
Total cases of tumor without proved malignancy	115	19	134	14.2
Carcinoma with metastases, proved malignancy	12	3	15	20.0
Total cases of true neoplasm	127	22	149	14.8
Hypertrophy and hyperplasia without neoplasm			11	

TABLE II

SUMMARY OF ISLET-CELL TUMORS
(Presbyterian Hospital Series, to March 15, 1944)

Number of patients explored		32
Tumor found in		27
Number of tumors removed		31
No tumor found		5
Tumor found at second operation		8
Postoperative deaths		3
adenoma	1	
questionably malignant	1	
von Gierke's disease	1	

TABLE III

PATHOLOGY OF TUMORS (TO MARCH 15, 1944)

Adenomas	16
Questionably malignant	8
Carcinoma	1
Adenomatosis	2
Total	27

Multiple tumors found in 4 patients.
Islet-cell tumors without hypoglycemia in two patients.

TABLE IV

LOCATION OF TUMORS

In head of pancreas	12
In body of pancreas	8
In tail of pancreas	10
In liver	1

TABLE V

SUMMARY OF OPERATIVE PROCEDURES

Excision of tumor	16
Partial pancreatectomy with tumor	5
Partial pancreatectomy without tumor	5
Removal of overlooked tumor	8
Simple exploratory	4

TABLE VI

RESULTS AFTER OPERATION (TO MARCH 15, 1944)

	CURED OF HYPOGLYCEMIA	IMPROVED	UNIMPROVED	POSTOPERATIVE DEATHS
Adenoma	15			1
Questionably malignant	72, 48, 24, 14, 12, 8, 4 mo. after operation			1
Carcinoma			Died 4 mo. later	
Adenomatosis	16, 5 mo. after operation			
von Gierke's disease				1
No tumor found		2	3	

TABLE VII

LENGTH OF THE FOLLOW-UP INTERVAL (TO MARCH 15, 1944)

	ADENOMAS	QUESTIONABLY MALIGNANT	ADENOMATOSIS	CARCINOMA
9 yr.	4			
8 yr.	1			
6 yr.	1	1		
5 yr.	2			
4 yr.	2	1		
2 yr.	1	1		
1 yr.	2	2	1	
Less than 1 yr.	2	2	1	

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THE ENDOCRINOLOGIC ASPECTS OF TUMORS OF THE PINEAL GLAND

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INTRODUCTION

THE pineal body was probably one of the earliest members of the endocrine series to be considered a glandular structure. In the second century Galen (quoted by Rowntree) stated: "It is in substance glandular. It was devised for the same purpose as other glands of the body." However, in spite of the extraordinary advances in the entire subject of endocrinology in the last few decades, the mystery of the pineal gland has remained unsolved. Even the question of its glandular nature, in spite of Galen's self-assurance, is to this day still a subject for debate. Experimental data are confusing and contradictory. The unique histologic appearance of this structure makes arguments by analogy with other glands of little value. Studies of pathologico-clinical states, especially tumors, which frequently have served to elucidate the normal function of an organ, have in the case of the pineal body appeared only to add to the confusion. With personal experience which includes five cases of tumor in the region of the pineal gland, I can offer no additional facts to the existing mass of material already in the literature. Indeed, there would be no excuse for this presentation if I were to accept a pronouncement published as recently as June, 1943, by Russell and Sachs: "This study offers no support for the concept that the pineal body is some form of endocrine gland." However, it is too simple to conclude that an organ has no function simply because we are unable to demonstrate what this function is. Too many glints of light from behind the curtain and too many intriguing fragments of unexplained data exist to allow one to be satisfied with a final judgment of a negative nature in this matter.

DEVELOPMENT AND STRUCTURE

In the human embryo, according to Bailey, the pineal gland first makes its appearance during the fourth or fifth week as an outpocketing of the roof of the diencephalon. In front of this a second part, consisting of a cell mass, appears, according to Krabbe. As the fetus develops, the cell mass enlarges and the fold becomes deeper but the two are separated by a connective tissue wall. The cavity in the fold is closed

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after the sixth fetal month. After this, the cells, which up to now have been round and undifferentiated, begin to enlarge with larger but paler nuclei containing less chromatin than before. This differentiation takes place in a scattered manner throughout the gland and continues to the end of the first year of extrauterine life. By this time the gland has taken on essentially the appearance of that of the normal adult in that it consists mostly of islands of these large cells surrounded by smaller cells with darker nuclei, among which a few scattered connective tissue fibers are found. The origin and function of these two types of cells are still the subject of controversy. Some authors believe that certain granules in the large cells indicate a secretory character, while Hortega thinks these granules are merely blepharoplasts. Nageotte, on the other hand, is convinced that gliosomes in the smaller cells are indicative of a secretory character. The origin of the latter cells is also disputed. Globus and Silbert, for example, consider them to be of mesenchymal origin, capable of differentiating into fibroblasts. Horrax and Bailey, on the other hand, believe them to be of neuroectodermal origin.

FUNCTION

Experimental Data.—Outside of certain Australian lizards in which the pineal gland has become highly specialized as a centrally placed rudimentary third eye, the function of the pineal gland has not yet clearly been defined. Speculation in the ancient world as by Galen was already mentioned, and in more recent times, the philosopher, Descartes, considered it as the seat of the soul. Modern experimental efforts to elucidate the function of this body have consisted of extirpation and transplantation experiments as well as feeding and parenteral administration of various forms of extract of the pineal gland.

Pinealectomy.—About nine years ago Andersen and Wolf analyzed the reports in the literature on pinealectomies done in various experimental animals, including rats, rabbits, dogs, chicks, and guinea pigs. Experiments were reported in all these animals with negative results by some workers and positive results by others. The positive results, when they occurred, were reported most commonly to be "premature developments of secondary sex characters in the male, enlargement of the gonads, overgrowth of the body, and obesity." After critically analyzing all these data, the previously named authors were inclined to be skeptical about these results and felt that the data submitted were not sufficient to justify the conclusions reached.

Feeding Experiments.—Rowntree reviewed the experiments reported by McCord, consisting of feeding fresh pineal glands to 400 young animals which he claimed caused early precocity and adiposity. Hoskins, on the other hand, found such feeding experiments to result in no changes whatever.

Pineal Implants.—In implantation of pineal glands, reviewed by Rowntree, Kozelka showed negative results in chicks, whereas Dubowik found increased rate of growth in rabbits. Lahr showed some retardation in the gonadal development in both male and female rats but no influence upon the body growth.

Injection of Pineal Extract.—No definite results of pineal extract injections had been demonstrated until Engel appeared to have found an antagonism of the pineal extract toward the growth hormone of the anterior lobe of the pituitary, as well as toward those pituitary hormones affecting luteinization and maturation of the ovarian follicles. Rowntree furthermore called attention to McCord's paradox, namely, that, according to the reports in experimental literature, extirpation of the gland leads to precocity of development, while the administration of pineal gland in excess leads in the young to eventually the same result by "hastening growth and sexual maturity."

In view of all this confusion, Rowntee and his co-workers introduced a new factor in the injection experiments. They tested the effect of pineal gland extract not only on the individual animals receiving the injections intraperitoneally, but also on the offspring of successive generations of parent rats. At the time of their report, five generations of pineal strain of rat had been under observation. In the first generation no effect was apparent other than moderate loss of weight and indication of excess sex excitation and early breeding. In the second generation, definite retardation of growth with mild precocity of gonadal development occurred. In the third to the fifth generation, changes along the same lines but much more clearly evident were seen, both in the retardation of growth and in the acceleration of gonadal and bodily development, leading them to coin the designation "precocious dwarfism," that is to say animals dwarfed physically but showing relative genital precocity. The dwarfed stature of these animals is permanent, but though small in size, they show an acceleration in the opening of their ears, the eruption of their teeth, the appearance of fur, the opening of their eyes, the descent of the testes, or the opening of the vagina. The average young rat of the fifth generation under pineal treatment is described as less than one-half the normal in size with both gonadal and bodily development occurring precociously. The penis particularly is described as relatively large compared to the body size; the teeth are erupted early and the eyes open in less than one-half the normal time. The animals, however, are physically weak, irritable, and nervous. The studies of Rowntree and his co-workers on many hundreds of rats are impressive not only in that they show an amplification of biologic effect in succeeding generations, but also in that these effects strongly suggest the endocrine character of the pineal glands in these animals. Their results are, nevertheless, difficult to translate into clinical terms. However, they suggest that the syndrome of Pellizzi, *macrogenitosomia praecox,* is an expression of *hyperpinealism.*

CLINICAL DATA FROM PINEAL TUMOR CASES

Patients with tumors occurring in the region of the pineal gland as reported in the literature have either shown no endocrinologic disturbances whatever or they have shown precocious pubertal development when the tumors affect young children, especially males. This syndrome described by Pellizzi is called macrogenitosomia praecox or pubertas praecox. Since it is the purpose of this communication to present only the endocrinologic aspects of tumor of the pineal gland, the five cases in my personal experience can be of little significance here except for the single case in which the previously named syndrome was present. The other four cases were those of two males and two females past the age of puberty who showed the classical neurologic signs of obstructive hydrocephalus with increased intracranial pressure and inability to rotate the eyes upward, which leads to a localization of a tumor mass in the region of the quadrigeminal plate in the neighborhood of the pineal gland. The fifth case was that of a 9-year-old boy with the syndrome of macrogenitosomia praecox which will be briefly presented here.

CASE REPORT

F. H. (N. I. No. 30702), male, 9 years of age, was admitted to the Neurological Institute of New York Oct. 23, 1936.*

Present Illness.—The patient was reported to be a normal healthy child until 9 or 10 months prior to admission, that is, January or February, 1936, at which time he began to have what at first was considered hoarseness but was later recognized as a distinct change in his voice, such as usually accompanies puberty. Within a short time thereafter, he developed pubic and axillary hair and rapid enlargement of both the penis and testicles. In March it was noted that he became mature-looking with a tendency to growth of a beard and soon thereafter he began to show some unsteadiness of gait. By May of 1936 he had gained twenty pounds since the onset of his illness. During the spring term at school, he began to show a distinct slump in his scholastic standing. By September, 1936, evidence of increased intracranial pressure was first noted in that he began to complain of severe frontal headache associated with vomiting, which was projectile in character. He also began to complain of double vision and his mother noted a strabismus which appeared about this time.

Physical Examination.—Examination revealed a 9-year-old boy acutely ill but presenting a most unusual physical appearance. He showed a relatively heavy growth of hair on the face as well as in the axillae and over the pubis and extremities. His "Adam's apple" was prominent and his voice had a distinctly adult low register. Although his height was compatible with his age, his penis and testicles were about average normal adult in size. No tumor of either testicle was present. Neurologically he showed bilateral papilledema with exudate and hemorrhages and pupils that were dilated and fixed to light and accommodation. There were left internal strabismus and right central facial paresis. The remainder of the neurologic examination was negative.

Laboratory findings were within normal limits. Roentgenograms of the skull showed only a calcific shadow of the pineal gland which, though somewhat unusual at 9 years of age, was not indicative of a tumor in this region.

*Grateful acknowledgment is hereby made to Dr. Tracy J. Putnam, Director, New York Neurological Institute, for permission to utilize this material.

He was operated upon Oct. 27, 1936, when a tumor of the pineal gland was revealed and part of it removed for examination. He was then given 3,000 roentgens through the open wound in the operating room, after all the tissues except the tumor had been carefully shielded by sterile lead sheeting. The patient recovered from the operation and signs of increased intracranial pressure were considerably improved. Unfortunately, during the night following the operation, he tore off the dressing and inserted his fingers into the wound. This was followed by an infection which gradually spread to involve the meninges and he died of meningitis Dec. 29, 1936.

*Post-Mortem Examination.**—The examination unfortunately was limited to the head only. This revealed, in addition to the infected wound and meningitis, a large tumor, best seen on sagittal section of the brain, measuring 5.3 by 5.2 cm. in diameter, occupying the upper one-half of the midbrain. The pineal gland was not discernible. The tumor compressed the anterior medullary velum and the anterior portion of the cerebellar vermis, the anterior surfaces of the cerebellar hemispheres, the dorsal aspect of the pons, the splenium of the corpus callosum, and the fornices (see Fig. 1). The tumor compressed the third ventricle posteriorly. The hypothalamus was distorted and foreshortened anteroposteriorly but was not directly impinged upon.

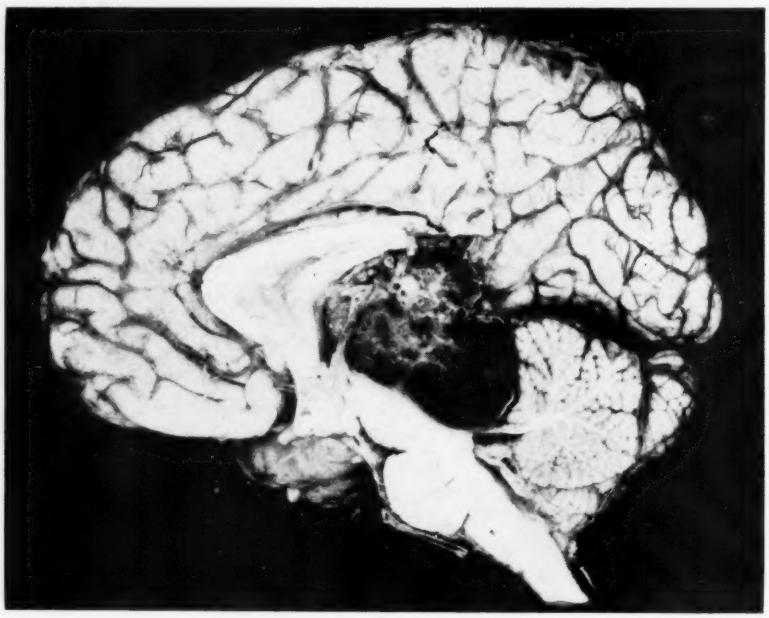

Fig. 1.—Sagittal section of brain showing large tumor in region of pineal.

Microscopically the tumor was found to be quite cellular, fairly vascular, with areas of hemorrhage and focal necrosis. The tumor cells were loosely arranged in small, irregular clusters which were separated by a vascular network and single or multiple rows of slender elongated cells. The predominating cell was irregular, polygonal, rarely rounded, occasionally having small processes. The cell cytoplasm was scanty, but the nuclei were large and round, oval, or slightly irregular with a moderate amount of finely granular chromatin and frequently a prominent nucleolus. Mitotic figures were commonly seen. Another type of cell less frequently encountered in the tumor was very large and irregular with abundant cytoplasm and large hyper-

*The author is indebted to Dr. Abner Wolf for the data concerning the pathologic appearances.

chromatic, often multiple, nuclei. The elongated cells, already mentioned, formed occasional bands of considerable width. Areas of necrosis, hemorrhage, and calcium deposition require no special description (see Fig. 2).

The pathologist concluded that the tumor was a complex neoplasm which he classified as a chorioepithelioma. Urine obtained by catheter post mortem gave a positive Friedman test. He was of the opinion that, in spite of the limited examination, the tumor was primary in the pineal region, rather than metastatic from somewhere else.

It is of passing interest perhaps that Boehner and Scarf, who reviewed the literature up to 1938, were able to find only one recorded case of chorioepithelioma of the pineal gland, reported by Askanazy.

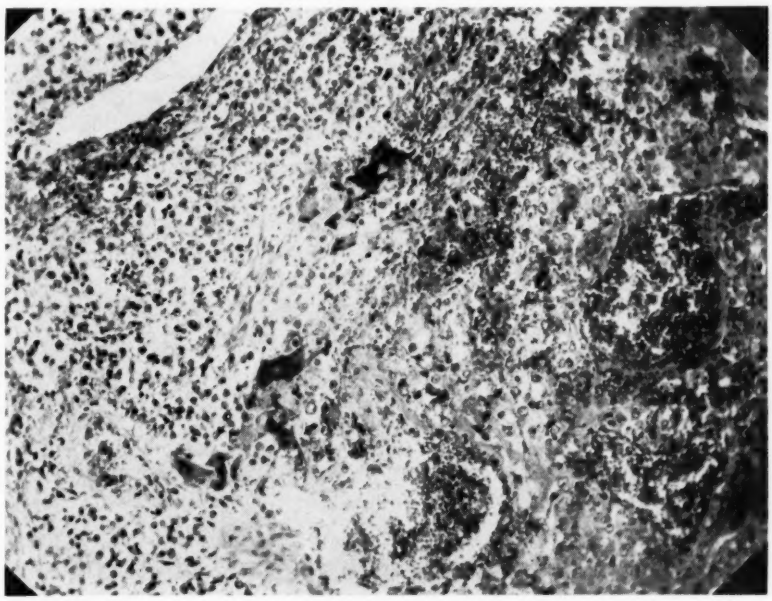

Fig. 2.—Photomicrograph (×60) showing general character of tumor.

COMMENTS

Although the picture of macrogenitosomia praecox is usually associated in the minds of most observers with a tumor of the pineal gland and usually the character of the tumor is considered that of a teratoma, these cases are nevertheless very rare. In 1925, Horrax and Bailey found only four cases in the literature and were able to add two more from Dr. Cushing's enormous material. In that report, however, they called attention to the case of Klaproth which was that of a boy of 15 years with a teratoma of the pineal gland who showed sexual infantilism rather than precocity. In 1928, Horrax and Bailey again added one more case of a probable pineal teratoma in which the patient showed pubertas praecox, but in the same article they reported another with an even more remarkable premature puberty in which the pineal was within normal limits, and a large tumor in the third ventricle histologically diagnosed as ganglioneuroma was found at operation and confirmed at

post-mortem examination. In 1938, Bochner and Scarf argued that the teratomatous tumors of the pineal gland may produce a premature sexual development in their victims by an effect similar to the stimulation of the ovaries in immature rabbits by urine obtained from pregnant women. They found some confirmation in this view in that the Aschheim-Zondek test is positive in males with teratomatous tumors of the testicles. Indeed, my own case illustrated the presence of a positive pregnancy test with a pineal tumor. Unfortunately, Bochner and Scarf's theory is exploded in the evidence presented by their case which was that of a 9-year-old boy who died of a teratomatous tumor of the pineal body and who showed no evidence of pubertas praecox. Moreover, pubertas praecox associated with a teratoma of the pineal gland in a female child is practically unknown, yet the pregnancy test is positive only when made on immature female animals.

DISCUSSION

The most widely accepted theory of the function of the pineal gland, as stated by Marburg, is that its secretory activity during the early years of life inhibits a development of puberty and that at the time of puberty the gland undergoes involution which thus removes its inhibitory effect and allows sexual development to take place. It was believed that the cases of macrogenitosomia praecox in which a large tumor destroying the pineal gland is present in early life might support this theory. However, we have Horrax and Bailey's case of a boy with a normal pineal gland and a tumor in the third ventricle not of pineal origin presenting the syndrome of premature puberty, and a similar case was reported by Schmalz. We have, moreover, the case reported by Horrax and Bailey in which the tumor of the pineal gland, which was associated with macrogenitosomia praecox, was not a teratoma but a pinealoma, reproducing in great abundance mature pineal tissue. Here it might be argued that even if the pineal gland were destroyed by the tumor, the tumor itself would more than supply the secretion of the gland. It may indeed be considered as evidence in this case that secretion of the pineal gland in excessive amounts initiates puberty rather than inhibits it. Further clinical support is lent to this theory by the prepubertal cases in which tumors other than teratoma or pinealoma occur and are not accompanied by premature puberty, for in these instances it may be argued the gland is actually destroyed and its secretion interrupted, and therefore no sexual changes accompany the tumor. A destructive tumor of the pineal gland associated with actual infantilism in the case reported by Klaproth, already mentioned, may be further evidence to point in this direction. Still another case supporting the point of view that the pineal secretion initiates puberty is that reported by Zandren, who described a case of infantilism that showed at necropsy no trace of the pineal body, even though this structure was searched by careful serial sections of the entire region.

How are we then to explain those teratomatous tumors which have been most commonly accompanied by premature puberty, since these tumors also destroy the pineal gland? Globus and Silbert believe that the marked variability in the histologic appearance of pineal tumors giving rise to a great variation in designation may be due to the different embryologic stages of the pineal body itself from which the tumors develop. They thus imply that even though tumors in the literature are often called "teratomas," they nevertheless are frequently pineal in origin. In view of the fact that these complex tumors may, therefore, originate from the pineal gland in its various stages of development, one might then assume some specific quality inherent in them, namely, a pineal-like secretion produced in sufficient amounts to initiate early puberty.

A further difficulty arises in attempting to explain on the basis of this theory Horrax and Bailey's case with a classical picture of macrogenitosomia praecox in a child with an apparently normal pineal and a large ganglioneuroma within the third ventricle. Here a possible explanation may exist in that the patient was demonstrated to have a normal-sized pineal gland which for some reason, perhaps associated with the abnormal hydrodynamics within the skull, was led to secrete abnormal quantities of hormone, producing an early development of puberty.

CONCLUSIONS

It is obvious from the foregoing that the problem of the pineal body is by no means solved. Even the question as to whether it is a gland or not is not wholly clear. On the other hand, it would seem to be possible to deduce, with less violence to the facts than by any other theory, from data obtained from the study of pineal tumors, that the pineal body is a gland of internal secretion with a hormone which apparently initiates puberty. This viewpoint moreover is supported by the most conclusive experimental data available up to this point, namely, that of Rowntree and his associates.

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Book Reviews

Medical Physics. By Otto Glasser, Editor-in-Chief, with 23 Associate Editors. Pp. 1744. Chicago, 1944, The Year Book Publishers, Inc.

The only appropriate description for this volume is monumental. It represents a great contribution to medical science literature in any language, and is one of a very few of comparable importance of American origin. More than 300 sections, each prepared by recognized original contributors to the numerous fields, present the various aspects of medical physics in a manner such as to make the volume a veritable mine of information and critical evaluation. It is at once indispensable for every scholarly clinician, a source book for investigators, and a handbook for the study of principles of physics and physical chemistry as they apply to biology and medicine. The title is not quite broad enough, unless one includes under "medical" everything fundamental to it, which the editors have obviously done. The volume actually represents a compendium of knowledge about biophysics in general, with special reference to medical problems.

The editors deserve nothing but praise for the useful work they have done in bringing so nearly all that is basic and useful in physics and physical chemistry into one volume for ready consultation. There are, of course, defects in the organization and presentation. There is lack of uniformity in practice about citation of references. The physics of gas flow in respiration is not adequately treated in the normal and pathologic subject. The problem of atelectasis is described without reference to alternative mechanisms of production, which in the opinion of many recent authors are more frequently causal than the one described. There are other instances of this type, and the editors will undoubtedly seek to improve the volume in many details in future editions, but the reviewer's opinion is that considering the scope of the work the defects are surprisingly few and the merits exceedingly great. As noted, the only principal improvement urgently indicated is a fuller bibliography. Aside from this a careful restudy of completeness of coverage of the various fields by the editors and their expert consultants is desirable.

The present volume serves a very real need and should be in the library of every physician with scholarly interests, as well as in every group medical library. The publishers are to be congratulated for their courage in risking the publication of this valuable book and in the generally excellent workmanship it embodies.

Intracranial Arterial Aneurysms. By Walter E. Dandy. Pp. 147. Ithaca, N. Y., 1944, Comstock Publishing Company, Inc.

This monograph consists of a systematic and comprehensive presentation of a difficult and little known clinical entity—intracranial arterial aneurysms—based on a study of 108 patients with 133 aneurysms. The subject is introduced by a general discussion of the incidence, types, symptoms and signs, and diagnostic procedures of intracranial arterial aneurysms. In the second chapter the cases are considered from the standpoint of an anatomic classification. A detailed analysis of each group is included in tabular form. The third chapter, by Dorcas Hager Padget, is devoted to the embryology and anatomy of the circle of Willis. In the fourth chapter the methods of preoperative ligation of the carotid and vertebral

arteries are described. The last chapter contains a discussion of the surgical treatment and operative results. Dandy was able to report cures in twenty patients in the series. An appended bibliography, tabulation of the series of cases, and perspicuous illustrations suggest the intensive research required in the preparation of this volume. The lack of an index is probably an intentional and perhaps not a serious omission, since the subjects are clearly indicated in the table of contents.

This compendium fills a definite need "in a seemingly barren field," which has actually proved, "with increasing confidence in diagnosis and with the correlated surgical follow-through" to be quite common, as the author has suggested in his preface.

The Year Book of General Surgery. Edited by Evarts A. Graham, A.B., M.D., Professor of Surgery, Washington University School of Medicine; Surgeon-in-Chief of the Barnes Hospital and of the Children's Hospital, St. Louis. Ed. 1. Pp. 736, with 270 illustrations. Chicago, 1944. The Year Book Publishers, Inc. $3.

The Year Book of Surgery is as large as in previous years and follows the same general scheme of treatment of a very broad subject matter. The items discussed under the caption of Military Surgery have increased in number, and throughout the volume emphasis has been given to the effects of trauma.

The editor states in the preface, "One of the regrettable casualties of war is its effect on scientific progress. What advance in science occurs is concerned chiefly with attempts to aid the actual conduct of fighting. There is no encouragement to pursue that sort of investigation which will make for better living or better health. The more nearly total the war becomes, the more striking will be its inhibiting effect on research that is unconnected with military affairs. Now in the fifth year of this total war it is apparent to anyone who reads the current literature that the amazing speed of scientific progress which characterized the last 50 years has been retarded to an appalling degree. How long this wave of depression will last cannot be foreseen."

There are new ideas and new procedures outlined in the 1943 Year Book and this rather gloomy note of the editor may appear a bit unduly pessimistic. As the editor implies, during time of war, all research, save that with a definite war-linked interest, of necessity comes to a virtual standstill. And it is through original experimental research that new facts are multiplied and the complexion of old and difficult problems changed.

The pertinent comments of the editor upon the published abstracts of papers are not as numerous as in some of the previous Year Books. Nevertheless, the volume is a good index of the surgical literature and warrants perusal by every surgeon.

Rehabilitation of the War Injured (A Symposium). By William Brown Doherty, M.D., and Dagobert D. Runes, Ph.D. Pp. 684, with 160 illustrations. New York, 1943, Philosophical Library, Inc. $10.

This book is a symposium to which contributions have been made by approximately fifty authors. The material is broken down under several different headings: Neurology and Psychiatry, Reconstructive and Plastic Surgery, Orthopedics, Physiotherapy, Occupational Therapy and Vocational Guidance, Legal Aspects of Rehabilitation, and Miscellaneous.

Largely due to the breadth of the field covered and to the number of contributors, there is unfortunately a considerable amount of overlap and repetition in the material presented. As a result, there is much more printed matter in the book than

there is any need to be. This tendency is unfortunately increased by a small number of chapters that seem entirely out of place.

There are many illustrations throughout the book, but most of them are of poor quality so that they do not have the value they should have. Reproductions of roentgen films, however, are satisfactory.

In contrast to the faults which have been listed, there are many excellent chapters by celebrated authors such as Denny-Brown, Cobb, Gillies, Smith-Petersen, Watson-Jones, and others. The material presented by this group is well organized and of great value to those in civilian practice quite as much as to those in the Armed Forces. A most interesting section is given to immersion-foot and allied ailments.

The volume contains some material that is not of much value, but this is more than outweighed by the large number of excellent sections included.

Pain Mechanisms. By W. K. Livingston, Lieutenant Commander, M.C., U.S.N.R., Assistant Clinical Professor of Surgery, University of Oregon Medical School, Portland, Ore. Ed. 1, Pp. 253, with 26 illustrations. New York, 1943, The Macmillan Company. $3.75.

This book consists of three parts. The first part is a discussion of the anatomy and physiology of pain. In this, the author lays the foundation for the main theme of the book, namely that intractable pain such as causalgia, other post-traumatic pain syndrome, low back disability, neuralgias, and phantom limb pain may be due to an internuncial pool of neurons in the cord. He infers that through increase in the phenomenon of facilitation and decreased inhibition in this internuncial pool, both being functions of this group of cells, ordinary nonpainful afferent impulses become painful.

The second part is concerned with the clinical syndromes of causalgia, post-traumatic pain syndromes, low back disability, facial neuralgias, chronic and phantom limb pain. This is the most valuable part of the book. The discussion of these conditions is good; the author has obviously had a large experience and many cases are described. Many patients received lasting relief from novocain injections. The possibility that when novocain injections are followed by lasting relief it may be due to suggestion is discussed but dismissed by the author. He is convinced that it is a mistake to assume that a certain pain syndrome must represent an obsession or be of purely psychic origin, simply because its manifestations do not conform to what we have been taught about the anatomy and physiology of peripheral nerve pathways. He believes that it is equally foolish to discredit the results of procedures such as periarterial sympathectomy and novocain injection on the ground that their mode of action is obscure.

The third part of the book is called Interpretations. It is composed of chapters on protopathic pain, hyperalgesia, the sympathetic component, and the vicious circle.

Protopathic pain is a discussion of Head's experiments and those of others who confirmed or refuted Head's notion of a special, primative type of nerve to account for protopathic pain. He finally concludes that anything that might act to disturb the normal pattern of impulses anywhere along their route from the periphery to the perceptual centers might lead to an unusual pattern of central excitation, and hence produce abnormal changes in sensory experience. A pathologic state of the internuncial pool within the spinal cord is suggested as one of the sites at which this distortion of sensory impulses might occur.

In the chapter on hyperalgesia, after discussing experimental work of various investigations on hyperalgesia, the author concludes that hyperalgesia may be due to modification of impulses anywhere between the periphery and sensorium, such as elaboration in the skin of some chemical substance which acts to increase the

sensitiveness of the skin locally, withdrawal of a part of the impulses which customarily constitute the composite of impulses underlying normal sensations derived from the skin, distortion of the intraneural pattern which results in fibers establishing new connections in regenerated nerves, abnormal sensations of the cells of the posterior horns of gray matter, lesions of the posterior columns, injuries of the brain in the region of the thalamus, or alteration in the status of the internuncial pool, the receiving station at the cord level.

Under sympathetic component the author points out that relief of causalgia cannot be due to section of afferent pain fibers in the sympathetic nerves, and that it is at least not always due to increased blood flow. Since elimination of either the trigger point or the sympathetic nerves alone may not give relief of the causalgia, he assumes that neither is the sole cause of the causalgic state. His assumption is that the barrage of abnormal impulses from an injured nerve acting on the internuncial pool of neurons in the cord disturb its normal functioning and this, in turn, disturbs the functioning of the sympathetic nerves and peripheral somatic nerves to produce peripheral changes from which abnormal afferent impulses arise to add themselves to those of the trigger point to sustain and augment the central activity.

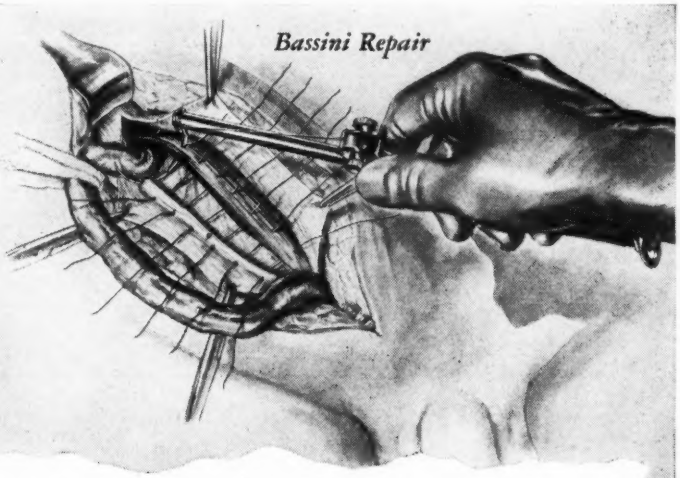
In the chapter on the vicious circle the author attempts to explain his concept of the vicious circle in causalgic states, and to compare it with the concept of the vicious circle as it is utilized by the psychiatrist to explain tension states. Essentially the difference he recognizes in the two is that psychic irritants set up a disturbed center chiefly at higher or cerebral levels, while in the causalgic state the disturbed center is primarily at least in the internuncial pool of the cord.

An organic lesion at the periphery, involving sensory nerve filaments, may become a source of chronic irritation. Afferent impulses from this trigger point eventually create an abnormal state of activity in the internuncial centers of the cord gray matter. The internuncial disturbances, in turn, are reflected in an abnormal motor response from both the lateral and anterior neurons of one or more segments of the cord. The muscle spasm, vasomotor changes, and other effects which this central perturbation of function brings about in the peripheral tissues may furnish new sources of pain and new reflexes. A vicious circle of activity is created. Thus, an ever-widening circle is set up and the advantage of treatment is obvious.

There are three reciprocating factors: the incoming impulses from the periphery; the internuncial pool activity; and the motor impulses from the lateral and anterior horn cells that are brought within the influence of the pool.

The author is congratulated upon writing a well-arranged and interesting book about these baffling clinical entities. His concept of the internuncial pool is theoretical and may be rejected, but the book contains many interesting and valuable observations.

It could be read with profit by almost any physician but should be of special interest to neuropsychiatrists, surgeons, and psychologists.



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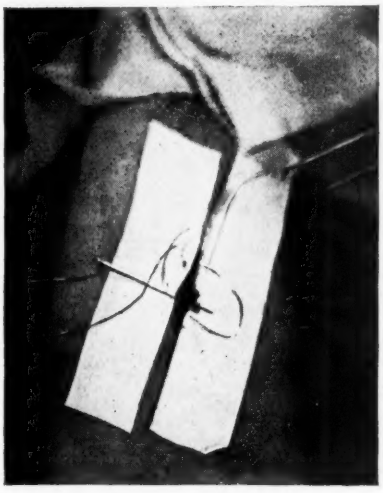

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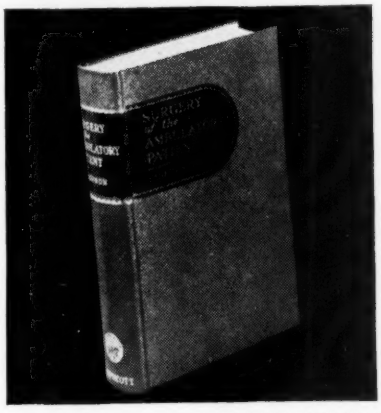

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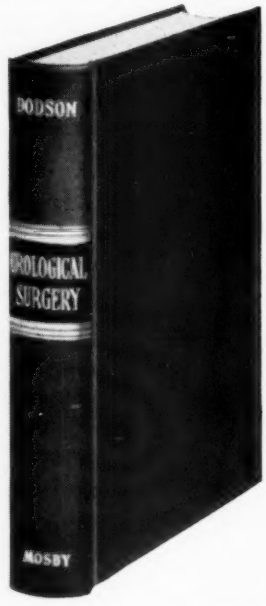

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